



## Sustained Release Formulations of Aceclofenac: A Brief Review

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### ABSTRACT

*Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects and play an important role in achieving the prolonged therapeutic effect of drug by continuously releasing medication over an extended period of time after administration of a single dose. Many drugs formulated in there sustained release pharmaceutical formulations for the effective treatment of disease or disorders. The Non-steroidal anti-inflammatory drugs (NSAIDs) are the important class of drugs used in various commercial pharmaceutical formulations for the effective treatment of chronic disorders. Aceclofenac is one of the important NSAID used for relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and alkylosing spondylitis and formulated in various sustained release dosage forms. Many research technologies have been developed for the design and formulation of sustained release dosage forms of Aceclofenac, which includes use of different types of polymeric matrix material and new methodologies were reviewed in present review along with its drug release profile.*

**Keywords:** Aceclofenac; Sustained release; Polymeric matrix; Rheumatoid arthritis; Non-steroidal anti-inflammatory

### INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates. The goal of sustained release drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then to maintain desired drug concentration. In this, the drug release will be maintaining the level of effect over an extended period of usually 8-12 hours or some times upto 24 hours. To maintain constant level of drug in to the system, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body for each drug this is a highly individualized quality [1].

Sustained release technology evolved with matrix technology. Several articles in the 1960s reported simple matrix tablets or monolithic granules. In 1952, a timed release formulation was developed by Smith Kline and French that launched a wide spread search for other applications in the design of dosage forms. Matrix tablets are the sensible choice for sustained release tablets. There has been a quest in the research community to develop a cost-effective, cheap excipient for controlling the release of drugs from such type of sustained release tablets [2].

Aceclofenac chemically, a phenyl acetic acid derivative, has anti-inflammatory and analgesic properties. It is a Non-steroidal anti-inflammatory drug (NSAIDs) used in various commercial pharmaceutical formulations for the treatment of fever, relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and alkylosing spondylitis

and reported to have good anti-rheumatic activity. Aceclofenac is the glycolic ester of Diclofenac. It is inhibitor of cytokine and works by blocking the action of a substance in the body called cyclooxygenase which involved in the production of prostaglandins and responsible for the generation of pain, swelling and their inflammatory conditions [3]. Aceclofenac is practically insoluble in water and soluble in alcohol & methyl alcohol, freely soluble in acetone & dimethyl formamide. The chemical structure of Aceclofenac Figure 1) [4].

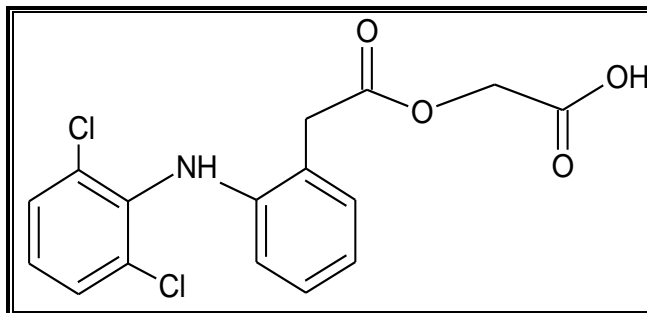


Figure 1: Chemical structure of Aceclofenac

Aceclofenac is suitable candidate for sustained release formulations because it exhibit neither very slow or very fast rates of absorption and excretion and also uniformly absorbed from the gastro intestinal tract and administered in relatively small doses with good margin of safety.

#### Advantages of sustained release formulations of Aceclofenac

1. Avoid repeated administration of drug dose and minimize the patient compliance
2. Minimise drug accumulation with chronic dosing.
3. Improve the efficiency treatment by controlling the conditions more promptly, reduce the fluctuations in drug level and improving the bioavailability.
4. Better control of drug absorption can be attained.
5. Safety margin with high potency can be increased and the incidence of both local and systemic adverse side effects can be reduced.

Many research methodologies have been developed for the design, formulation and evaluation of Aceclofenac sustained release dosage forms which includes the use of polymeric matrix materials of synthetic and natural origin or in combination of both with different sustained release of drug were outlined in brief as follows:

Basavaraj *et al.*, have developed and evaluated sustained release formulation of Aceclofenac based on monolithic matrix technology. The tamarind seed polysaccharide was utilized and wet granulation technique was used to prepare tablets. Tamarind seed polysaccharide acts as hydrophilic and rate controlling polymer. The *In-vitro* release study of matrix tablets was carried out in phosphate buffer pH 7.4. The prepared tablets showed 98.062% drug release upto 12 hours [5].

D Gaikwad *et al.*, have reported formulation and evaluation of sustained release tablet of Aceclofenac by film coating. Sustained release tablet of Aceclofenac was prepared by using Hydroxy Propyl Methyl Cellulose polymer (HPMC). The formulated tablet was evaluated for its physicochemical properties and *In-Vitro* release studies [6].

S Gosh *et al.*, have reported preparation and evaluation of Aceclofenac sustained release formulation and its comparison with marketed product. The oral controlled release of Aceclofenac matrix tablet was prepared using various viscosity of hydrophilic polymer HPMC in two different proportions with hydrophobic polymer ethyl cellulose and gour gum. Wet granulation technique used to prepare matrix tablet and drug release was studied by using *In-Vitro* method [7].

KPR Chowdary *et al.*, have developed formulation of Aceclofenac tablet employing starch phosphate – a new modified starch. A new modified starch was prepared, characterized and evaluated as a carrier in solid dispersion for enhancing the dissolution rate of Aceclofenac. Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperature. Solid dispersion of Aceclofenac in starch phosphate was prepared by solvent evaporation method [8].

KS Prabha *et al.*, have reported preparation and *in vitro* evaluation of sustained release microspheres of Aceclofenac. The microspheres of aceclofenac was prepared by emulsion cross linking method and solvent evaporation technique by using different grades of gelatin with varying concentrations and Eudragit (S-100, L-100) polymers respectively. The optimized formulation showed good *in-vitro* sustained release activity of Aceclofenac [9].

H Panikkarakayil *et al.*, have developed sustained release Aceclofenac matrix tablets constituting Kollidon sustained release (KSR) (polyvinyl acetate and povidone-based matrix retarding polymer). The matrix tablets were prepared by dry blending and direct compression method and exponential model was applied to characterize the drug release behavior from polymeric systems. They found that non-Fickian release is predominant in tablets containing KSR with a trend toward zero-order kinetics. The release rate was determined by *in vivo* evaluation as well as *in vitro* experiments [10].

SK Uma Devi *et al.*, have developed colon specific drug delivery systems for Aceclofenac using chitosan as a microbially degradable polymeric carrier. The pH dependent polymeric coating solution containing Eudragit L 100 and S 100 (1:4) was used to coat the formulation [11].

B Rastogi *et al.*, have developed Aceclofenac loaded chitosan microspheres which showed promising results for a sustained release during an enhanced time duration. Controlled release microsphere was prepared using chitosan by ionotropic gelation method. Chitosan acts as mucoadhesive and biodegradable polymer. The prepared formulation was submitted for its *In vitro* release profile and evaluated for *In-Vivo* Anti - Inflammatory activity [12].

A Mohsen *et al.*, have developed sustained release matrix tablets of Aceclofenac with Eudragit® RSPO and Eudragit® RLPO using three techniques; direct compression, wet granulation and solid dispersion. The most optimum matrix formula was manipulated by addition of an immediate release layer for prompt release of the drug. Prepared tablets were evaluated regarding their physical properties and *in-vitro* release over 24 hours. *In-vitro* release studies revealed that Eudragit RSPO retarded the release more than Eudragit RLPO and solid dispersion was the most suitable preparation technique. Pharmacokinetic studies in albino rabbits were conducted for optimization [13].

Md A Habib *et al.*, have developed sustained release matrix tablets of Aceclofenac using eggshell powder as newly investigated pharmaceutical excipient. Two different eggshell powders treated with ethanol and chloroform was used. The treated samples were prepared by surface modification using 1.0 % w/v stearic acid in solvent namely deionized water, 95 % ethanol and chloroform. Dissolution studies of formulations in pH 6.8 phosphate buffer was performed using USP Dissolution Apparatus II which indicates that chloroform treated eggshell powder containing formulation showed most amendable sustain release over 24 hours than ethanol treated eggshell powder containing formulation [14].

AC Shaikh *et al.*, have developed once daily sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like hydroxy propyl methyl cellulose K -100. The drug release from optimized formulations was extended for a period of 24 hrs. The optimized formulations were subjected to stability studies for one month at 45° temperature with RH 75±5% [15].

SK Vijaya *et al.*, have developed sustained release drug delivery systems of Aceclofenac using citrus gum by wet granulation technique. Sustained released tablets of were prepared with citrus gum powder and compared with hydroxyl propyl-methyl cellulose (HPMC) K-100 [16].

AKL Kabir *et al.*, have developed a sustained release matrix tablet of Aceclofenac using hydroxy propyl methylcellulose (HPMC K15M and HPMC K100M CR) in various proportions as release controlling factor by direct compression method. The *in-vitro* dissolution study was carried out for 24 hours using United States Pharmacopoeia (USP) 22 paddle-type dissolution apparatus in phosphate buffer with pH 7.4 [17].

V Dave *et al.*, have prepared ocular inserts of Aceclofenac by using hydroxy propyl methyl cellulose and ethyl cellulose alone and in combination. *In-vitro* transcorneal permeation study was carried out by using a goat cornea. The results showed that 98.24% of drug was released from the formulation containing 3% HPMC and for 3% ethyl cellulose 70.25% of drug was released for a period of 24 hours with zero order kinetics. Medicated inserts also subjected to UV irradiation and *In-vivo* ocular irritation studies [18].

HA Ahad *et al.*, have developed matrix tablets of Aceclofenac with *Prosopis juliflora* gum. The dissolution study proved that the dried *Prosopis juliflora* gum can be used as a matrix forming material for making once daily sustained release matrix tablets [19].

T Bisht *et al.*, have developed matrix and triple layer matrix tablets of Aceclofenac sodium using natural polymer gum acacia as matrix forming agent and cross povidone as immediate layers. The triple layer matrix tablet showed better sustained effect as compare to plain matrix tablet [20].

S Ghosh *et al.*, have developed matrix tablets for oral controlled release of Aceclofenac using various viscosity of hydrophilic polymer HPMC. The hydrophobic polymer ethyl cellulose and Guar gum was prepared by wet granulation method and subjected to *in vitro* drug release studies in pH 7.5 phosphate buffer medium and results obtained showed that optimized formulation gives controlled release action comparable with marketed sustained release tablet formulation of Aceclofenac (Aeroff-SR) [21].

A Arunachalam *et al.*, have developed sustained release tablets of Aceclofenac using different natural polymers like Guar gum and Xanthan gum and Chitosan by direct compression technique. The prepared tablets were subjected to *In-vitro* study and bioequivalence studies. The results of *In-vitro* drug release studies showed that optimized formulation showed sustained release action of drug (98.47%) when compared to marketed product (73.52%) for 24hrs [22].

MV Laxmi *et al.*, have developed modified release matrix tablets of Aceclofenac by wet granulation method, using ethyl cellulose and calcium acetate phthalate. Ethyl cellulose acts as sustained release polymer and calcium acetate phthalate as a pH dependent polymer [23].

A Gandhi *et al.*, have reported matrix tablet of Aceclofenac for its sustained release action in order to overcome their side effects by conventional dosage form. The melt granulation method using hydrophobic waxes was used to prepare tablets. The release profile of prepared formulation was studied using dissolution studies [24].

G Gandhiji *et al.*, have developed sustained release matrix tablets of Aceclofenac (200mg) by direct compression using hydrophilic polymer like hydroxy propyl methyl cellulose k100 and hydroxy propyl methyl cellulose and hydroxy propyl methyl cellulose k100 and ethyl cellulose 20cps. *In-vitro* release was performed using phosphate buffer of pH 7.4 for 24hrs which showed that hydroxy propyl methyl cellulose k30 and ethyl cellulose 20cps both is best suitable for sustained release formulation by direct compression method [25].

BV Basavaraj *et al.*, have developed sustained release tablets of Aceclofenac using isolated mucilage powder of *Plantago ovate* and they have compared its efficiency with hydrophilic matrix polymer HPMC K4 M. The sustained drug release was found to be up to 12 hours in optimized formulation which was better than HPMC K4 MZ [26].

T Ramasamy *et al.*, have developed a colon targeted drug delivery systems for Aceclofenac using xanthan gum as a carrier. Multilayer coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes was designed to achieve effective colon delivery of Aceclofenac. The release profile of drug in simulated gastrointestinal fluid and colonic fluid with enzymes were studied [27].

A Kaushik *et al.*, have developed micro pellet formulations in order to attain the instantaneous release of Aceclofenac in the gastrointestinal tract which would enhance gastric residence time with increased absorption from the stomach & intestine to produce sustained pharmacological responses along with reduced dosing frequency and ultimately the bioavailability would also increase. *In-vitro* release study of formulation was carried out using pH 1.2 HCl, pH 7.0 phosphate buffers, simulated gastric and intestinal fluids. The optimized formulation contains 1:1 ratio of Aceclofenac: gellan gum [28].

S Muthalik *et al.*, prepared sustained release tablets of Aceclofenac by direct compression using hydroxy propyl methyl cellulose –K4M. By comparing the dissolution profiles with the marketed product, the tablet containing HPMC (45%) and MCC (30%) along with talc and magnesium stearate (1%w/w, each) was considered as better formulation [29].

RK Deshmukh *et al.*, have developed polymeric microspheres containing Aceclofenac by single emulsion (oil-in-water) solvent evaporation method using response surface methodology (RSM). Microsphere was prepared by changing formulation variables such as the amount of Eudragit® RS100 and the amount of polyvinyl alcohol (PVA) by statistical experimental design. The microspheres showed high E.E. (74.14±0.015% to 85.34±0.011%) and suitably sustained drug release (minimum; 40% to 60%; maximum) over a period of 12h. The optimized microspheres formulation showed E.E. of 84.87 ± 0.005 with small error value (1.39) [30].

A Sharma *et al.*, in their study they have designed once daily sustained release tablet of Aceclofenac using HPMC of various grades as polymer as release retarding agent. Dissolution study was carried out in phosphate buffer pH 6.8 media and compared with marketed preparation. The prepared formulation contains Aceclofenac to HPMC K 15M in the ratio of 200: 23 (in mg) and found to show sustained release upto 24 hour [31].

Kannan *et al.*, have developed and evaluated once daily sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like hydroxy propyl methyl cellulose K -100. The prepared tablets were subjected to physicochemical studies, *in-vitro* drug release, kinetic studies and stability studies. The drug release from optimized formulations was extended for a period of 24 hours. The optimized formulations were subjected to stability studies for one month at 45°C temperature with RH 75±5% and showed there was no significant change in drug content, physicochemical parameters and release pattern [32].

CR Gupta *et al.*, have reported formulation and evaluation of once daily sustained release tablets of Aceclofenac using polyethylene oxides of different molecular weights as matrix polymers. The direct compression method was used to prepare polyethylene oxides matrices. They have used 28% of PEO (80% PEO WSR 303 and 20% of PEO WSR N60K) as matrix which showed similar release profiles, as that of marketed product, Hifenac SR [33].

S Basak *et al.*, have reported formulation and evaluation of enteric coated Aceclofenac matrix tablets using hydroxy propyl methyl cellulose polymer. Tablets were prepared by wet granulation technique. The drug to polymer ratio in prepared formulation was 1:0.47. and showed sustained release upto 12 hours [34].

S Dey *et al.*, have developed bilayer tablets of Aceclofenac and it was characterized by initial burst drug release followed by sustained release of drug. They have used microcrystalline cellulose (MCC) and HPMC K4M as the polymers material and the optimization of sustained release formulation was done on the basis of 3<sup>2</sup> factorial designs. The double layer tablets of Aceclofenac were found to be effective for once-a-day oral-controlled release drug delivery system [35].

Khan *et al.*, have reported formulation of bilayer matrix tablets containing Aceclofenac as sustained release using HPMC as the matrix forming polymer. *In-vitro* drug release study was carried out in hydrochloric acid buffer of pH 1.2 (0.1N) with 1% w/v SLS using USP paddle apparatus and release rate was estimated using validated UPLC-PDA method. The sustained release effect was observed for 12 hours [36].

KM Manjanna *et al.*, have prepared and evaluated calcium alginate microbeads with calcium chloride as cross-linking agent for Aceclofenac sodium using ionotropic external gelation method. The mean particle size of drug-loaded microbeads was in the range of 596.45±1.04 to 880.10±0.13. The drug entrapment efficiency was obtained in the range of 63.24±0.66 to 99.75±0.87. *In-vitro* drug release profile of microbeads was found to be pH dependent and it was analyzed by different kinetic models [37].

Different methods used for preparation of sustained release formulation of Aceclofenac along with polymers used were briefly outlined in table 1.

**Table 1: Methods/Techniques and polymers used for preparation of Aceclofenac sustained release dosage forms**

Sl. No.	Type of Dosage Forms	Methods/ Technique	Polymers
1	Matrix Tablet	Monolithic matrix technology	Tanarind seed polysaccharide
2	Matrix Tablet	Wet granulation	Hydroxyl Propyl Methyl Cellulose (HPMC)
3	Matrix Tablet	Solvent evaporation and solid dispersion	Starch phosphate
4	Matrix Tablet	Dry blending and direct compression	Kollidon sustained release polymer (polyvinyl acetate and povidone based matrix retarding polymer)
5	Matrix Tablet	Direct compression, wet granulation and solid dispersion	Eudragit RSPO and Eudragit RLPO
6	Matrix Tablet	Wet granulation	HPMC K-100
8	Matrix Tablet	Direct compression	HPMC K15 M and HPMC K100MCR
9	Matrix Tablet	Wet granulation	HPMC and ethyl cellulose
10	Matrix Tablet	Direct compression	Gour gum, xanthan gum, chitosan
11	Matrix Tablet	Wet granulation	Ethyl cellulose and calcium acetate phthalate
12	Matrix Tablet	Melt granulation	Hydrophobic waxes
14	Matrix Tablet	Direct compression	HPMC K4M
15	Matrix Tablet	Wet granulation	Hydrophilic polymer line HPMC K100
16	Matrix Tablet	Direct compression	Polyethylene oxides (PEOS)
17	Matrix Tablet	Wet granulation	HPMC
18	Bilayer Matrix Tablet	Wet granulation	HPMC K4M and Microcrystalline Cellulose
19	Microbeads	Ionotropic external gelation method	Calcium alginate microbeads and calcium chloride cross linking agents.
20	Polymeric Microbeads	Single oil in water emulsion solvent evaporation method using surface methodology	Eudragit
21	Microspheres	Ionotropic gelation method	Chitosan
22	Microspheres	Emulsion cross linking and solvent evaporation	Eudragit

## CONCLUSION

This review presents various methods for development and evaluation of sustained release formulation of Aceclofenac. Different types of methods, polymers and various excipients used to prepare Aceclofenac sustained released formulation were described along with its release profile and it was found that use of synthetic and natural polymers play an important role in formulation. The use of hydroxy profile methyl cellulose was found to be more as a polymeric matrix in most of the formulation.

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