

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ACECLOFENAC TABLETS PREPARED BY SOLID DISPERSION BY USING MANNITOL

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ABSTRACT

Aceclofenac is new nonsteroidal anti-inflammatory drug acting by an inhibition of the synthetic of prostaglandins by inhibiting the activity of the enzyme, cyclooxygenase-2 (COX-2). It is more selective for COX-2 than COX-1. Aceclofenac is practically insoluble in water and peak blood level rebase between 1.25 to 3 hrs after oral administration. It is practically insoluble in aqueous fluids. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water-soluble drugs. To improve the dissolution of aceclofenac through the formulation of solid dispersion using water soluble carriers like mannitol by melt solvent methods and to convert the optimized solid dispersion in fast dissolving tablet formulation. The formulated tablets showed rapid in vitro drug dissolution and dissolution efficiency within 30 min.

Key words: Aceclofenac; Mannitol; Fast dissolving Tablet; Solid dispersion.

INTRODUCTION

Aceclofenac is new nonsteroidal anti-inflammatory drug acting by an inhibition of the synthetic of prostaglandins by inhibiting the activity of the enzyme, cyclooxygenase-2^{1,2,3}(COX-2). It is more selective for COX-2 than COX-1⁴. Aceclofenac is preferred over conventional NSAIDs as they may lead to serious gastrointestinal complications such as ulcer, severe bleeding and perforation, resulting in hospitalization and even death⁵. It is mainly used for the osteoarthritis, rheumatoid arthritis and dysmenorrhea⁶. The drug is available in tablets dosage form and is yet not official in any pharmacopoeia

except B.P. Aceclofenac is practically insoluble in water and peak blood level rebase between 1.25 to 3 hrs after oral administration. It is practically insoluble in aqueous fluids.

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37° C) due to erratic or

incomplete absorption from gastrointestinal tract (GIT)⁷. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water-soluble drugs. Numbers of drug have been shown to improve their dissolution character when converted to solid dispersion⁸⁻¹². Some reports on the formulation of these systems have appeared¹³. Because of its poor aqueous solubility Aceclofenac may pose dissolution related absorption problem. In context of the above principles, a strong need is felt to developed a solid unit dosage form that deliver aceclofenac in the GIT in a form that dissolve very rapidly to reduce its onset time to produce quick pharmacological effect.

Thus an attempt is made in the present investigation to improve the dissolution of aceclofenac through the formulation of solid dispersion using water soluble carriers like mannitol and by melt solvent and solvent evaporation methods and to convert the optimized solid dispersion in fast dissolving tablet formulation.

Fast dissolving drug delivery system

A fast dissolving drug delivery system (FDDDS) can be defined as a dosage form for oral administration, which when placed in mouth, rapidly disintegrates or dissolves and can be swallowed in the form of liquid. Conventional dosage form is very popular in pharmaceutical industries because of its easy transportation and low manufacturing cost. However for pediatrics and geriatrics fast dissolving tablet is preferred due to its swallowing conveniences.²²

Advantages of fast dissolving drug delivery system

It offer ease of administration for pediatrics, geriatrics, mentally ill, and uncooperative.

It require no water intake

It shows quick disintegration and dissolution of the dosage form.

It overcomes unacceptable taste of the drugs.

It can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.

Introduction to Solid dispersion system²⁴

It is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent or melting solvent method. The solid dispersion may also be called solid-state dispersion. Dispersion obtained through the fusion process is often called melts and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates. The two basic procedures used to prepare solid dispersion the fusion and cosolvent techniques. Modification of these method and combination of them has also been used.

Method of solid dispersion preparation²⁵

Solid dispersion can be prepared by different method based on the physical properties and thermal stability of the drug and the carriers.

Melting or fusion method

A physical mixture of an active agent and a water-soluble carrier is heated until it is melted. The melt is rapidly solidified in ice bath under rigorous stirring. The fused mass is then pulverized and sieved. Rapid congealing is desirable because it results in super saturation of drug as a result of entrapment of solute molecules in the solvent matrix by instantaneously solidification. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss. Spray congealing from a modified spray drier onto a cold metal surface has also been used. Product from spray congealing can be obtained in pellet form without the necessity of a grinding step that may alter crystalline modification.

Solvent method

Physical mixture of two solid components is dissolved in a common solvent and then the solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate is critical to the quality of the dispersions. A mixture of solvent may also be used. Freeze-drying and spray drying can also achieve the solvent removal. This method is also called co-precipitation. Co

precipitation is a recognized technique for increasing the dissolution of poorly water-soluble drugs such as Ketoprofen, spironolactone, nifedipine, so as to consequently improve their bioavailability.

Melting-solvent method

It has found that 5-10 % w/w of liquid compound could be incorporated in PEG 6000 without significant loss of its solid properties. Hence it is possible to prepare solid dispersion by first dissolving drug in a suitable solvent and then the solution is incorporated directly into the melt of PEG (70 ° C) without removing the liquid solvent.

MATERIALS AND METHODS

Determination of UV absorption maxima

Aceclofenac solution was prepared in phosphate buffer pH 6.8 and diluted suitably. The UV spectrum of the solution was taken on Shimadzu UV-1601 UV/Vis double beam spectrophotometer. The solution exhibited UV maxima at 275.0 nm as shown in figure 1.1.

Preparation of calibration curve

Accurately weighed 10 mg of aceclofenac was transferred to a 100 ml volumetric flask and dissolved in 60 ml phosphate buffer pH 6.8. The volume was adjusted to the mark with phosphate buffer pH 6.8 to prepare stock solution (0.1 mg/ml). Aliquots of working solution of aceclofenac (0.5 – 3 ml, 100 µg/ml) were transferred in to a series of 10 ml volumetric flasks and volume was made up to the mark with phosphate buffer pH 6.8. The absorbance of the resulting solution were measured at 275.0 nm against a reagent blank solution prepared similarly without drug using Shimadzu UV/ Vis double beam spectrophotometer. Calibration curve was prepared by plotting concentration versus absorbance.

The method was validated for linearity, accuracy and precision. The method obeys Beer-Lambert's law in the concentration range of 5–30 µg/ml. The results of standard curve preparation are shown in Table 1.1 and Figure 1.2.

Preparation of solid dispersion of aceclofenac with carriers

Solid dispersion containing aceclofenac and carrier in the proportion of 1:1, 1:2, 1:3, and 1:4 were prepared by melt solvent. Solid dispersion of drug with mannitol was prepared by melt solvent method. In this method, aceclofenac was dissolved in acetone and the solution was incorporated into the melt of mannitol at 165° C by pouring into it. It was kept in an ice bath for sudden cooling. The mass was kept in the desiccators for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through 80#. All the solid dispersion was preserved in well-closed glass container till use.

Infrared absorption spectroscopy

Infrared absorption spectroscopy (IR) spectra of aceclofenac (fig.1.3), mannitol (fig 1.4), and solid dispersion of aceclofenac and mannitol (fig.1.5) are shown. Infrared absorption spectroscopy (IR) of aceclofenac showed sharp band at 3319, 3278 and 1770 cm^{-1} due to stretching vibration bands of OH, NH, and C=O, respectively. Solid dispersion (SD) prepared using solvent evaporation method at 1:3 ratio showed decrease in intensity and shift to higher wave number for 3319 and 3270 cm^{-1} . This finding suggested that there might be a short of molecular interaction of the drug and mannitol in SD. Formulations of tablets of aceclofenac-mannitol by solid dispersion given in Table 1.2

Cumulative percentage of aceclofenac release from formulated tablets with Mannitol given in Table 1.3, In vitro release profile of aceclofenac from formulated tablet with mannitol given in Figure 1.6. Tablets formulations were developed from aceclofenac – mannitol solid dispersion (1:4) that has shown maximum in vitro dissolution rate. But there is minor difference in dissolution rate between solid dispersion (1:4) and (1: 3). Croscarmellose sodium used as a disintegrating agent. sodium lauryl sulphate (1%) and magnesium stearate (1%) were used as a glidant – lubricant. The average weight of tablet was adjusted to 500 mg using lactose and Hydroxypropyle cellulose (HPC) in

equal proportion. All the ingredients were mixed intimately and the mixture was compressed into tablets (500mg weight) on a rotary tablet machine. The formulated tablets were stored in a tightly closed glass container and evaluated for various characteristics.

Evaluation of solid dispersion tablets

Compressed tablets were then evaluated for hardness¹⁵, disintegration¹⁶, friability¹⁷ and drug content. Monsanto types hardness tester measured hardness. One tablet was placed in each tube of disintegration apparatus (model ED, Electrolab) media at $37 \pm 2^{\circ}$ C. Friability was determined in friabilator by taking twenty tablets. For drug content analysis twenty tablets were accurately weighed and finely powdered. Quantity of powder equivalent to 100 mg of aceclofenac was taken into a 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. 5 ml of the filtrate was diluted to 100 ml with phosphate buffer pH6.8. and assayed for drug content at 275.0 nm using double beam UV / Vis. Spectrophotometer (Shimadzu, model – 2201). The average drug content of the tablets found was $102 \pm 0.2\%$. Table (1.4) shows the evaluation of tablets of aceclofenac. Results of formulated aceclofenac tablets batch S4 given in Table 1.4.

In vitro dissolution study of aceclofenac tablets

In vitro dissolution study of tablets^{18, 19} was conducted using USP dissolution apparatus II (model TDT-06T, Electrolab) at 50 rpm, using phosphate buffer pH 6.8 as a dissolution media maintaining at $37 \pm 0.5^{\circ}$ C. Sample were withdrawn 5 ml, at 5 min. intervals to 30 min. and filtered through a filter paper, diluted and assayed at 275 nm using UV/ Vis double beam spectrometer.

Comparison of prepared aceclofenac tablet with marketed tablets

The developed tablet formulation was compared with conventional market tablet for in vitro drug release profile and % dissolution efficiency²⁰. Percentage of drug dissolved in 30 min (Q_{30}) and dissolution efficiency after 30 min (DE_{30}) were consider

for comparison. Results are shown in Table 1.5. The in vitro release profile of batch S4 was compared with conventional market tablet (CMT) for similarity factor (f_2) and dissimilarity factor²¹ (f_1). The data are shown in table 1.6.

RESULT AND DISCUSSION

Results of analytical method

Aceclofenac solution exhibited UV maxima at 275.0 nm as shown in Figure 1.1 Developed method was validated for linearity, accuracy and precision. The method obeys Beer-Lambert's law in the concentration range of 5 – 30 μ m with a correlation coefficient of 0.9947 (Table 1.1) indicating good linearity in this concentration range. The proposed method is simple, sensitive, accurate and precise and can be employed as a quality control tool for the estimation of aceclofenac in its tablets and in bulk drug.

Results of in vitro dissolution study of the prepared tablets

Table 1.3 show the cumulative percentage of aceclofenac released from formulations. It is clear that the dissolution of aceclofenac has improved considerably in mannitol using formulation. The poor dissolution of pure drug could be due to poor wettability and / or agglomeration of particles. Figure 1.6 shows the in vitro release profile of aceclofenac from mannitol using formulation having different weight ratios of mannitol such as 1,2,3,4, for 1 part of aceclofenac and pure drug. Release profile shows that dissolution of aceclofenac increase with increase in drug; mannitol ratio up to 1:3. Increase in the dissolution rate may be due to improved wettability by the carrier. No marked changes on dissolution appear at higher ratio (1: 4). That may be due to distortion of molecular dispersion structure which leaves an insoluble base particle and increased accumulation of carrier molecule in the bulk to cause a saturation by which further solubility of aceclofenac is retarded. This mannitol using formulation used for further evaluation.

Results of evaluation of formulated tablets

Compressed tablets were evaluated for hardness, disintegration, friability and drug content (Table 1.4). Mean hardness and mean disintegration time of the tablets was found to be 3 Kg/cm³ and 15 sec respectively. Percentage friability and % assay were found 0.42 and 102.8 ± 0.2, respectively and were within the acceptable limit.

Result of comparison of prepared aceclofenac tablets with marketed tablets

The developed tablet formulation (formulation S4) was compared with conventional market tablet (CMT A), (CMT B), and (CMT C) tablet for in vitro drug release profile (Q₃₀) and % dissolution efficiency (DE₃₀). The Q₃₀ values of conventional marketed tablet (CMT A), (CMT B), (CMT C) and formulation S4 were 49.31, 70.47, 80.46, 81.42 and 95.32 respectively. (Table 1.5, figure 1.7) indicating betterness of formulation S4. The DE₃₀ values were 23.17, 53.13, 62.26, 59.50 and 69.79 respectively. (Table 1.5, figure 1.7) indicating betterness of formulation S4. The in vitro release profile of formulation S4 was compared with conventional market tablet (CMT A), (CMT B), and (CMT C) for

similarity factor (f₂) and dissimilarity factor (f₁). The values for f₁ for (CMT A), (CMT B), and (CMT C) are 21.94, 11.33, and 13.07 respectively and f₂ for (CMT A), (CMT B), and (CMT C) are 36.33, 49.77 and 47.09 (Table 1.6) indicating no similarity in in vitro dissolution of formulation S4 with (CMT A), (CMT B), and (CMT C). There for formulation S4 was considered better cost effective formulation with higher and rapid in vitro dissolution.

CONCLUSION

The study demonstrates the preparation of fast dissolving aceclofenac tablets containing its solid dispersion by using mannitol as a carrier. The polymer used in the solid dispersion and its concentration had significant effect on the in vitro dissolution of the drug from solid dispersion. The formulated tablets showed rapid in vitro drug dissolution and dissolution efficiency within 30 min. The developed tablets were able to produce rapid onset of action of the drug with reasonable cost.

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Table 1.1: Data for calibration curve of aceclofenac in phosphate buffer pH 6.8 at 275 nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Average
0	0	0	0	0.00
5	0.162	0.164	0.163	0.163
10	0.279	0.278	0.280	0.279
15	0.389	0.391	0.390	0.390
20	0.518	0.519	0.517	0.518
25	0.615	0.614	0.615	0.615
30	0.724	0.723	0.722	0.723
Correlation Coefficient = 0.9947 Absorbance = 0.0238 x + 0.0328				

Table 1.2: Formulations of tablets of Aceclofenac-mannitol by solid dispersion

Ingredients in (mg)	S1	S2	S3	S4	S5
Aceclofenac	100	100	100	100	100
Mannitol	-	100	200	300	400
Hydroxypropyl cellulose	50	50	50	50	50
Croscarmellose sodium	30	30	30	30	30
Magnesium stearate	5	5	5	5	5
Sodium lauryl sulphat	5	5	5	5	5
Lactose monohydrate	310	210	110	10	10
Total	500	500	500	500	600

Table 1.3: Cumulative percentage of Aceclofenac release from formulated tablets with Mannitol

No	Time (min)	S1	S2	S3	S4	S5
1	0	0	0	0	0	0
2	5	8.7	14.86	31.99	53.73	55.43
3	10	14.96	25.43	40.66	64.92	67.58
4	15	22.76	36.97	51.13	75.65	74.94
5	20	29.1	46.45	62.66	84.23	85.03
6	25	38.87	55.85	66.55	91	92
7	30	49.31	61.18	77.48	94.82	96.58
8	60	61	76.96	85.87	97.91	98.74

Table 1.4: Results of formulated Aceclofenac tablets batch S4

S.No	Evaluation parameters	Results
1	Mean hardness (Kg / cm ²)	3.0
2	Mean disintegration time (sec)	15
3	Friability %	0.42
4	Assay %	102 ± 0.2

Table 1.5: Comparison of formulation S4 with marketed aceclofenac tablets

Product	% Drug release After 30 min (Q ₃₀)	% Dissolution efficiency After 30 min (DE ₃₀)
Pure drug	49.31	23.17
Market product (CMT) A	70.47	53.13
Market product (CMT) B	80.46	62.26
Market product (CMT) C	81.42	59.50
Formulation S4	95.32	69.79

DE₃₀: Dissolution efficiency after 30 min. CMT A: is a conventional market tablet from Medley pharmaceutical Ltd. CMT B: is a conventional market tablet from IPCA pharmaceutical Ltd. CMT C: is a conventional market tablet from Intas pharmaceutical Ltd.

Table 1.6: Cumulative % drug release of batch (S4) and marketed product

Time (min)	Formulation S4	CMT A	CMT B	CMT C
0	0	0	0	0
5	53.73	43.18	45.45	51.5
10	64.92	56.52	61.68	55.85
15	75.65	54.87	72.34	62.14
20	84.23	62.65	75.78	71.89
25	91	66.36	78.11	74.94
30	94.82	70.47	80.46	81.42
60	97.91	84.83	84.72	90.98
Similarity factor (f ₂)		36.33	49.77	47.09
Dissimilarity factor (f ₁)		21.94	11.33	13.07

CMT A: is a conventional market tablet from Medley pharmaceutical Ltd
 CMT B: is a conventional market tablet from IPCA pharmaceutical Ltd
 CMT C: is a conventional market tablet from Intas pharmaceutical Ltd.

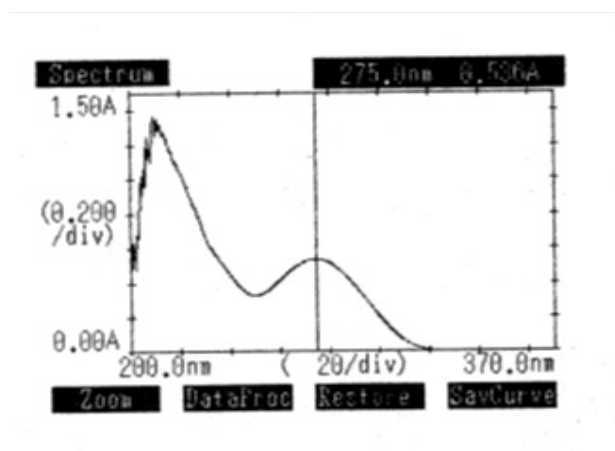


Fig. 1.1: UV spectrum of aceclofenac

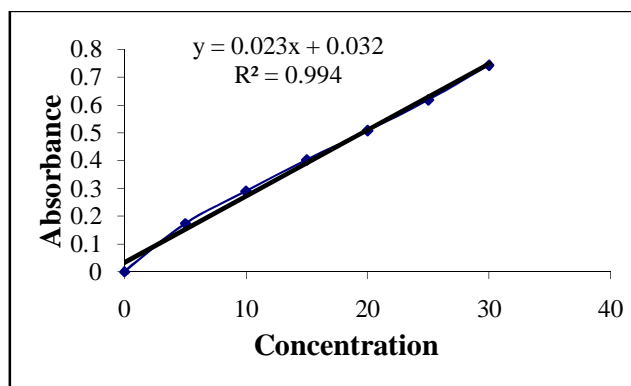


Fig. 1.2: Calibration curve of aceclofenac in phosphate buffer pH 6.8 in phosphate buffer pH 6.8

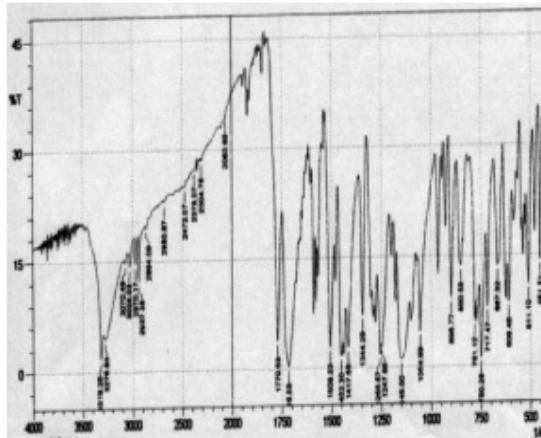


Fig. 1.3: Infrared spectra of aceclofenac

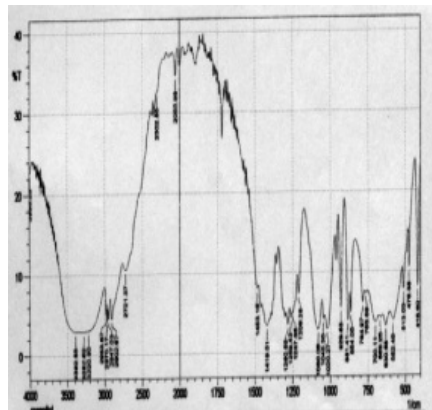


Fig. 1.4: Infrared spectra of mannitol

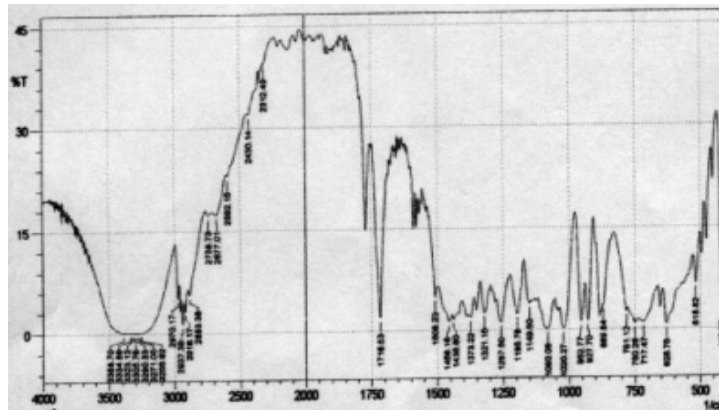


Fig. 1.5: Infrared spectra of solid dispersion of aceclofenac-mannitol (1:3)

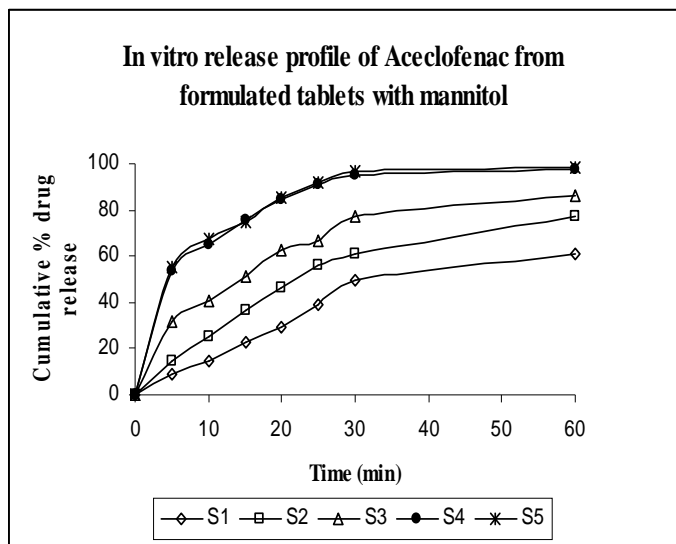


Fig. 1.6: In vitro release profile of aceclofenac from formulated tablet with mannitol

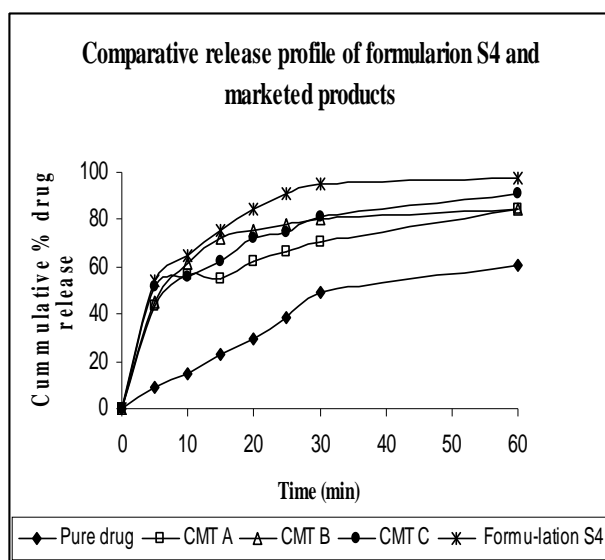


Fig. 1.7: In vitro release profile of aceclofenac from formulation S4 and marketed product

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