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FORMULATION AND *IN VITRO* EVALUATION OF ACECLOFENAC SOLID DISPERSION

Y. Ankamma chowdary*[1] and Venkata suresh jilakara[2]

[1*]Department of Pharmaceutics, NRI College of Pharmacy, Pothavarappadu, Agiripalli, Krishna district, Andhra Pradesh, India.

[2]Department of Pharmacognosy and Phyto Pharmaceutical, KLR Pharmacy College, Contractor's colony, Paloncha, Khammam, Andhra Pradesh, India.

ABSTRACT

The approach of solid dispersion for improving the dissolution of poorly soluble drugs. Aceclofenac, was selected as a model for the study, by using Mannitol as carrier and give more rapid onset of action compared to oral conventional dosage form to improve bioavailability and patient compliance. Solid dispersion of Aceclofenac and Mannitol was prepared by Physical mixture, Melting method and Melt solvent method by different ratios (1:1, 1:2, 1:3, and 1:4) and evaluated by FTIR, DTA analyses and *in vitro* dissolution characteristics. Dispersions prepared by melting method show better dissolution profile than dispersions prepared by melt solvent method and physical mixture. This may be due to grinding; there is a uniform distribution of drug in the polymer crust at molecular level in a highly dispersed state. Thus, when such system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increases the dissolution surface available. There is an enhancement of dissolution of Aceclofenac on increasing the concentration of Mannitol. As per the results represented for Trial-4, it is obvious that Aceclofenac: Mannitol (1:4) is proved to possess enhanced dissolution profile.

KEYWORDS

Aceclofenac, Mannitol, Solid dispersion, Physical mixture, Melting method and Melt solvent method.

Author for Correspondence:
Y. Ankamma chowdary,
Department of Pharmaceutics,
NRI College of Pharmacy, Pothavarappadu,
Agiripalli, Krishna district, Andhra Pradesh, India.

Email: yarlagaddaac@yahoo.co.in

INTRODUCTION

Orally administered drugs should undergo dissolution in the gastro-intestinal fluids before absorption can commence. Insoluble or poorly soluble drugs are generally poorly absorbed from the gastro-intestinal tract after oral administration. The absorption behavior of such drugs can be best studied by *in vitro* dissolution characteristics. In other words, *in vitro* dissolution is considered the index of *in vivo*

absorption of poorly soluble drugs[1]. Solid dispersion is a unique approach to present a poorly soluble drug in an extremely fine state of subdivision to the gastro intestinal fluids. It can be prepared by fusion, co-precipitation and kneading methods. This dispersion consist of microcrystalline dispersion of the poorly soluble drug in a matrix consisting of physiologically inert, readily water soluble solids. Exposure of this type of solid dispersion system to the gastrointestinal fluids results in dissolution of water soluble matrix (carrier). As the matrix dissolves, it exposes the dispersed poorly soluble drug in an extremely fine state of subdivision, to the aqueous gastrointestinal fluids. Hence the poorly soluble drug is presented to the aqueous fluids in a form which facilitates its dissolution rate and bioavailability[2].

Dissolution is the rate-limiting step for the absorption of poorly soluble drugs. Several researchers have employed different methods to improve the dissolution behaviour of such drugs. Use of adjuvant, use of salts, pH effect, particle size reduction, polymorphism, crystal form, use of solvates and hydrates, complexation, use of surface active agents, drug-excipient interaction and solid dispersion are the methods adopted to improve the dissolution characteristics of these drugs[3].

Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption always is dissolution rate limited. Sekiguchi and obi[4] were the first to report an improved dissolution of the drug from sulfamethazole-urea solid dispersion. Following their findings, more works in this direction were carried out. The enhanced dissolution of poorly soluble drugs such as griesiofulvin[5], chloramphenicol[6], naproxen[7] and triamterene from solid dispersion has been well documented. In the recent past, similar studies have been performed on glibenclamide, clofibrate, zolpidem, albendazole, allopurinol and promising results were reported. Solid dispersion releases the drug through different mechanisms and the rate of release of the drug to the surrounding fluid is dependent on the type of the solid dispersion formed. Solid dispersion can form either a eutectic mixture or solid solution or glass solution or amorphous precipitation in a crystalline carrier or compound or complex formation.

MATERIALSAND METHODS

Material

Aceclofenac was obtained as a gift sample from Amoli organics Ltd, Mumbai. Mannitol as a gift sample from Qualigens fine chemicals, Mumbai. All the ingredients used were of analytical grade.

Method

Preparation of solid dispersions and physical mixtures of Aceclofenac

There are several carriers, which have been reported for the preparation of solid dispersions by using various methods of preparation described earlier. The following carriers were selected depending upon suitability of carriers like Mannitol was selected for their efficiency in increasing the dissolution rate of Aceclofenac.

Preparation of physical mixtures

Accurately weighed quantities of drug and carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number 100# and was stored in desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: Polymer ratios of 1:1, 1:2, 1:3 and 1:4 were prepared.

Preparation of solid dispersions

Melting method

In melting method, accurately weighed quantities of Aceclofenac and Mannitol were taken in a mortar and mixed in some time. Then this physical mixture was transferred into a china dish and was melted on a sand bath. The fusion temperature was controlled 165 to 175 ^{0}C. The melted mixture was immediately cooled and solidified in on ice bath with vigorous stirring. The mass obtained was scrapped, crushed, pulverized and passed through sieve number 100#. The obtained

product was stored in desiccators.

Melt solvent method

In melt solvent method, required quantity of Mannitol was taken in a china dish and melted on a water bath. Then accurately weighed quantity of Aceclofenac was taken and dissolved in ethanol or methanol. The prepared solution was poured into the melt of mannitol at 165 ^{0}C. The china dish was kept on an ice bath for sudden cooling. The solidified mass was scrapped, crushed, pulverized and passed through sieve number 100#. The obtained product was stored in a dessicator.

EVALUATION PARAMETERS

Evaluation of Aceclofenac solid dispersions

Fourier transform infrared spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide disks using thermon electron FTIR. Samples were prepared in potassium bromide discs by means of a hydrostatic press. The scanning range was 400 to 4000 cm $^{-1}$ and the resolution was 4cm^{-1}. IR spectroscopy has been to quantify the interaction between drug and carrier FTIR spectra of pure Aceclofenac: Mannitol (1:4) (MM), Aceclofenac: Mannitol (1:4) (MM).

Differential thermal analysis (DTA)

DTA patterns of samples were obtained with Schimadzu DTA-50 instrument using vented aluminium pans. For DTA analysis each sample of 5-10 mg weight was taken in hermetically sealed flat-bottomed aluminium pans. The sample was heated over a temperature range of 30-300 ^{0}C in nitrogen atmosphere (30 ml/min) at constant rate of 10 ^{0}C. The instrument was calibrated with standard medium. Differential thermal analysis of Aceclofenac, Mannitol and Aceclofenac: Mannitol (1:4) (MM).

Estimation of drug content

A quantity, which was equivalent to 10 mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in pH 6.8 phosphate buffers. For both the sample and standard solutions absorbance was measured at 275 nm in UV-Visible spectrophotometer.

***In vitro* dissolution study**

The prepared solid dispersions were subjected to *in vitro* dissolution. Dissolution test was carried out using USP23 paddle method [apparatus-2]. The stirring rate was 50 rpm, pH-6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5^{0}C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Aceclofenac at 275 nm by using UV-visible spectrophotometer are shown at Table No.3, 4, 5 and 6.

Kinetics of drug Release

The mechanism of drug release from the Mannitol-Aceclofenac solid dispersions and tablets during the dissolution test in dissolution medium, (pH-6.8 phosphate buffer) was determined using zero order and first order.

Zero order equation

It describes systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fit into the zero order equation:

$$Q = Q_0 - K_0 t$$

Q=Amount of drug released at time‘t’

Q_0=Amount of drug released initially (often considered zero)

K_0=Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes. Zero order plots is derived from plotting the cumulative percent drug dissolved vs. time.

First order equation

The first order equation describes the release from

systems where dissolution rate is dependent on the concentration of the dissolving species. The dissolution data of tablet formulations in dissolution medium that is water containing pH 6.8 phosphate buffer were plotted in accordance with the first-order equation, i.e., the logarithm of the percent remained as a function of time.

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303$$

C_0=Initial concentration of the drug

C=Concentration of drug at time‘t’

K=First order constant, t =Time

Dissolution Efficiency

DE is defined as the area under the dissolution curve up to a certain time‘t’ expressed as percentage of the area of the rectangle described by 100 % dissolution in the same ‘t’.

$$\text{Dissolution Efficiency (DE)} = \left[\frac{\int_0^t y.dt}{y_{100}.t}\right] 100$$

The dissolution efficiency can have a range of values depending on the time intervals chosen. In any case, constant time intervals should be chosen for their comparison. For example, the index DE_{20} would relate to the dissolution of the drug from a particular formulation after 20 minutes and could only be compared with DE_{20} of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

RESLTS AND DISCUSSION

Pre-formulation Studies

Physical mixture of drug and carrier was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Aceclofenac were found to be unaltered in the spectra of the drug-polymer physical mixture (Figure No.1-3).

Differential thermal analysis

Differential thermal analysis of pure Aceclofenac and Mannitol (1:4) shown in (Figure No.6). Differential thermal analysis of pure Aceclofenac scanning range from 142 ^{0}C to 170 ^{0}C shown in (Figure No.4). The DTA diagram of pure Aceclofenac sharp endothermic peak at 153.13 ^{0}C. Differential thermal analysis of Mannitol scanning range from 156.33 ^{0}C to 179.14 ^{0}C shown in (Figure No.5). The DTA diagram of Aceclofenac sharp endothermic peak at 166.76 ^{0}C. Differential thermal analysis of ACE: Mannitol (1:4) MM scanning range from 151.26 ^{0}C to 171.14 ^{0}C. The DTA diagram of Aceclofenac: Mannitol. Sharp endothermic peak of Aceclofenac at 153.13 ^{0}C and Mannitol at 166.76 ^{0}C.

Estimation of drug content

A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 50 ml pH 6.8 buffer of was added and then the solution was subjected to sonication for about 2 hrs. The solution was made up to the mark with pH 6.8 buffer. The solution was filtered and suitable dilutions were prepared with pH 6.8 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 275 nm by using UV-Visible spectrophotometer.

***In vitro* dissolution studies**[8]

Aceclofenac and Solid dispersions were prepared by taking different weight ratios of Aceclofenac: Mannitol [(1:1), (1:2), (1:3) and (1:4)] by using physical mixture, melt solvent method and by melting method. The dispersions were subjected to *in vitro* dissolution studies in the dissolution medium (6.8 pH phosphate buffer) to select the optimized solid dispersion possessing enhanced *in vitro* dissolution.

In trial-01

Aceclofenac: Mannitol dispersions were prepared in the ratio of 1:1 by MS and MM. The results of trial-01 are shown in Table No.3 and Figure No.7 and 11. In the conjugates prepared by melt solvent method the drug release was 58 % in 60 min while in conjugates

prepared by melting method the drug release was 61.24 % at the end of one hour. The result was not sufficient. For further drug release concentration of mannitol was increased in next trial.

In trial-02

For improving the drug release profile over previous trial, concentration of mannitol was increased. Then Aceclofenac: Mannitol conjugates were prepared in the ratio of 1:2 by melt solvent and by melting method. The results of trial-02 are shown in Table No.4 and Figure No.8 and 12. The conjugates prepared by melt solvent method gave drug release only 62.18 % in 60 min and by melting method gave drug release only 62.18 % in 60 min. In this trial, the drug release was more when compared to previous trial. For enhancing the drug release increased the concentration of mannitol in the next trial.

In trial-03

Aceclofenac: Mannitol dispersions were prepared in 1:3 ratios. The results of trial-3 are shown in Table No.5 and Figure No.9 and 13. The dispersions, which were prepared by melt solvent method, the drug release was 68.20 % in 60 min while in conjugates prepared by melting method, drug release was 73.58 % at the end of 1st hour. This trial gave more drug release when compared to previous trial.

In trial-04

Aceclofenac: Mannitol dispersions were prepared in 1:4 ratios. The results of trial-4 are shown in Table No.6 and Figure No.10 and 14. The dispersions, which were prepared by melt solvent method, the drug release was 78.58 % in 60 min while in conjugates prepared by melting method, drug release was 99.68 % in 45 min. This trial gave more drug release when compared to previous trial. Dissolution of Aceclofenac was increased in carrier dispersions prepared by physical mixture, melt solvent method and by melting method when compare to pure drug.

Dispersions prepared by melting method show better dissolution profile than dispersions prepared by melt solvent method and physical mixture. This may be due to grinding; there is a uniform distribution of drug in the polymer crust at molecular level in a highly dispersed state. Thus, when such system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increases the dissolution surface available. Moreover, other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction may be attributed to better dissolution profile. The enhancement of dissolution of Aceclofenac from solid dispersions may be due to the amorphous nature of the drug in solid dispersions.

There is an enhancement of dissolution of Aceclofenac on increasing the concentration of Mannitol. As per the above results represented for Trial-4, it is obvious that Aceclofenac: Mannitol (1:4) (MM) is proved to possess enhanced dissolution profile.

Dissolution efficiency (DE_{20})

Dissolution efficiency values were calculated by the method suggested by Khan and shown in Table No.11. DE_{20} values were calculated from cum % Drug Released vs. Time plots. The solid dispersions prepared with Aceclofenac: Mannitol (MM) 1:4 ratio showed the highest dissolution rate and efficiency (54.37) with low $t_{1/2}$ value (5.57) when compared to other solid dispersions. Dissolution of the Aceclofenac from solid dispersions followed first order dissolution rate. The dissolution rate after 60 min was examined by plotting a Log (% Drug Retained) vs. Time. A linear relationship was obtained. The dissolution rate constant was calculated from the slope of the regression line. The first order dissolution rate constant for Aceclofenac: Mannitol (MM) 1:4 and Aceclofenac were 0.1243 K (min^{-1}) and 0.0046 K (min^{-1}).

Table No.1: General composition of formulation

S. No	Solid dispersion methods	Drug: Carrier	Ratio
1	Physical mixture	Aceclofenac: Mannitol	1:1 1:2 1:3 1:4
2	Melt solvent method		1:1 1:2 1:3 1:4
3	Melting method		1:1 1:2 1:3 1:4

Table No.2: Drug content of prepared solid dispersions and physical mixtures (Average of three determinations)

S.No	Solid dispersion methods	Drug: Carrier	Ratio	% of Aceclofenac present
1	Physical mixture	Aceclofenac: Mannitol	1:1 1:2 1:3 1:4	99.0 99.5 98.0 97.8
2	Melt solvent method		1:1 1:2 1:3 1:4	99.0 98.5 98.0 99.5
3	Melting method		1:1 1:2 1:3 1:4	97.5 99.0 99.5 98.0

Table No.3: Dissolution data of Pure Aceclofenac and Aceclofenac: Mannitol (1:1)

S. No	Time (min)	Cumulative % drug release(X±S.D)*			
		Pure Drug	P.M	M.S	M.M
1	0	0	0	0	0
2	5	13.10±0.36	21.12±0.98	24.88±0.26	28.10±1.32
3	10	21.12±0.98	26.26±0.85	30.10±0.98	36.12±1.02
4	15	24.62±0.94	28.18±0.53	38.80±0.68	40.88±0.65
5	30	30.88±0.23	34.60±0.98	40.26±0.65	46.12±0.95
6	45	36.92±0.65	39.82±0.65	44.80±0.12	53.42±0.12
7	60	40.10±0.58	50.10±1.4	58.0±1.02	61.24±0.98

*** Mean± S.D, n=3**

P.M- Physical Mixture, M.S- Melting Solvent method, M.M- Melting method

Table No.4: Dissolution data of Pure Aceclofenac and Aceclofenac: Mannitol (1:2)

S. No	Time (min)	Cumulative % drug release(X±S.D)*			
		Pure Drug	P.M	M.S	M.M
1	0	0	0	0	0
2	5	13.10±0.36	23.80±1.02	28.10±0.95	30.18±0.28
3	10	17.82±1.02	29.92±0.69	32.80±0.32	41.02±0.82
4	15	24.62±0.94	31.00±0.56	40.10±0.12	48.00±0.32
5	30	30.88±0.23	34.90±0.21	45.18±0.54	52.80±0.25
6	45	36.92±0.65	44.18±0.95	51.62±0.32	58.92±0.95
7	60	40.10±0.58	55.10±0.65	62.18±0.85	67.18±0.63

*** Mean± S.D, n=3**

Table No.5: Dissolution data of Pure Aceclofenac and Aceclofenac: Mannitol (1:3)

S.No	Time (min)	Cumulative % drug release(X±S.D)*			
		Pure Drug	P.M	M.S	M.M
1	0	0	0	0	0
2	5	13.10±0.36	26.18±0.65	31.86±0.98	36.54±1.02
3	10	17.82±1.02	32.82±0.26	35.18±0.26	45.80±0.65
4	15	24.62±0.94	34.42±0.35	44.10±1.52	54.92±0.95
5	30	30.88±0.23	40.10±0.12	48.24±0.85	59.10±0.25
6	45	36.92±0.65	46.72±0.85	55.10±0.69	61.82±0.89
7	60	40.10±0.58	58.82±0.32	68.20±0.51	73.58±1.25

*** Mean± S.D, n=3**

Table No.6: Dissolution data of Pure Aceclofenac and Aceclofenac: Mannitol (1:4)

S.No	Time (min)	Cumulative % drug release(X±S.D)*			
		Pure Drug	P.M	M.S	M.M
1	0	0	0	0	0
2	5	13.10±0.36	29.18±1.03	39.10±0.65	48.46±1.05
3	10	17.82±1.02	40.97±0.32	51.45±0.26	61.12±0.98
4	15	24.62±0.94	49.62±0.64	59.23±0.94	72.20±0.28
5	30	30.88±0.23	58.12±0.12	68.32±0.81	94.10±0.65
6	45	36.92±0.65	62.11±0.98	71.88±0.25	99.68±0.69
7	60	40.10±0.58	65.21±0.65	78.58±1.02	----

***Mean± S.D, n=3**

Table No.7: *In vitro* dissolution kinetic data for the pure drug

S.No	Drug	Slope	R^2	K(min^{-1})
1	Aceclofenac	0.002	0.953	0.0046

Table No.8: *In vitro* dissolution kinetic data for the physical mixtures

S.No	Drug: Carrier	Ratio	Slope	R^2	K(min^{-1})
1	Aceclofenac: Mannitol	1:1	0.003	0.973	0.0069
2		1:2	0.003	0.971	0.0069
3		1:3	0.004	0.955	0.0092
4		1:4	0.005	0.891	0.0115

Table No.9: *In vitro* dissolution kinetic data for the melt solvent method

S.No	Drug: Carrier	Ratio	Slope	R^2	K(min^{-1})
1	Aceclofenac: Mannitol	1:1	0.003	0.909	0.0069
2		1:2	0.004	0.952	0.0092
3		1:3	0.005	0.946	0.0115
4		1:4	0.006	0.926	0.0138

Table No.10: *In vitro* dissolution kinetic data for the melt method

S.No	Drug: Carrier	Ratio	Slope	R^2	K(min^{-1})
1	Aceclofenac: Mannitol	1:1	0.004	0.977	0.0092
2		1:2	0.005	0.972	0.0115
3		1:3	0.006	0.950	0.0138
4		1:4	0.007	0.957	0.1243

Table No.11: DE_{20}, DP_{10} and $t_{1/2}$ of solid dispersions and physical mixtures

S.No	Sample	Ratio	DE_{20}	DP_{10}	$t_{1/2}$ (min)
1	Aceclofenac	-	17.18	17.82	150.45
2	Aceclofenac: Mannitol (PM)	1:1	23.43	26.26	100.30
		1:2	25	29.92	100.30
		1:3	28.125	32.82	75.22
		1:4	36.25	40.97	60.18
3	Aceclofenac: Mannitol (MS)	1:1	28.75	30.10	100.30
		1:2	30.93	32.80	75.22
		1:3	33.75	35.18	60.18
		1:4	45.31	51.45	50.15
4	Aceclofenac: Mannitol (MM)	1:1	31.56	36.12	75.22
		1:2	30.62	41.02	60.18
		1:3	41.25	45.80	50.15
		1:4	54.37	61.12	5.57

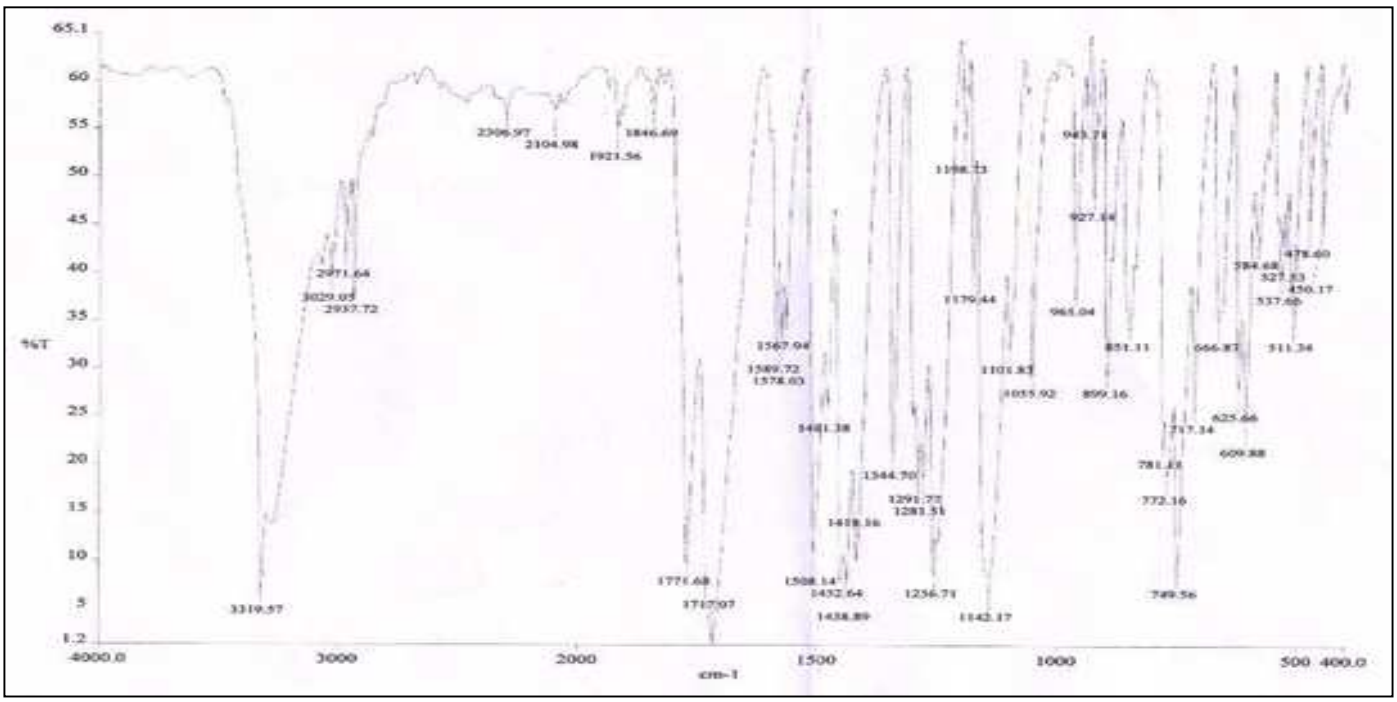

Figure No.1: FT-IR spectra of pure Aceclofenac

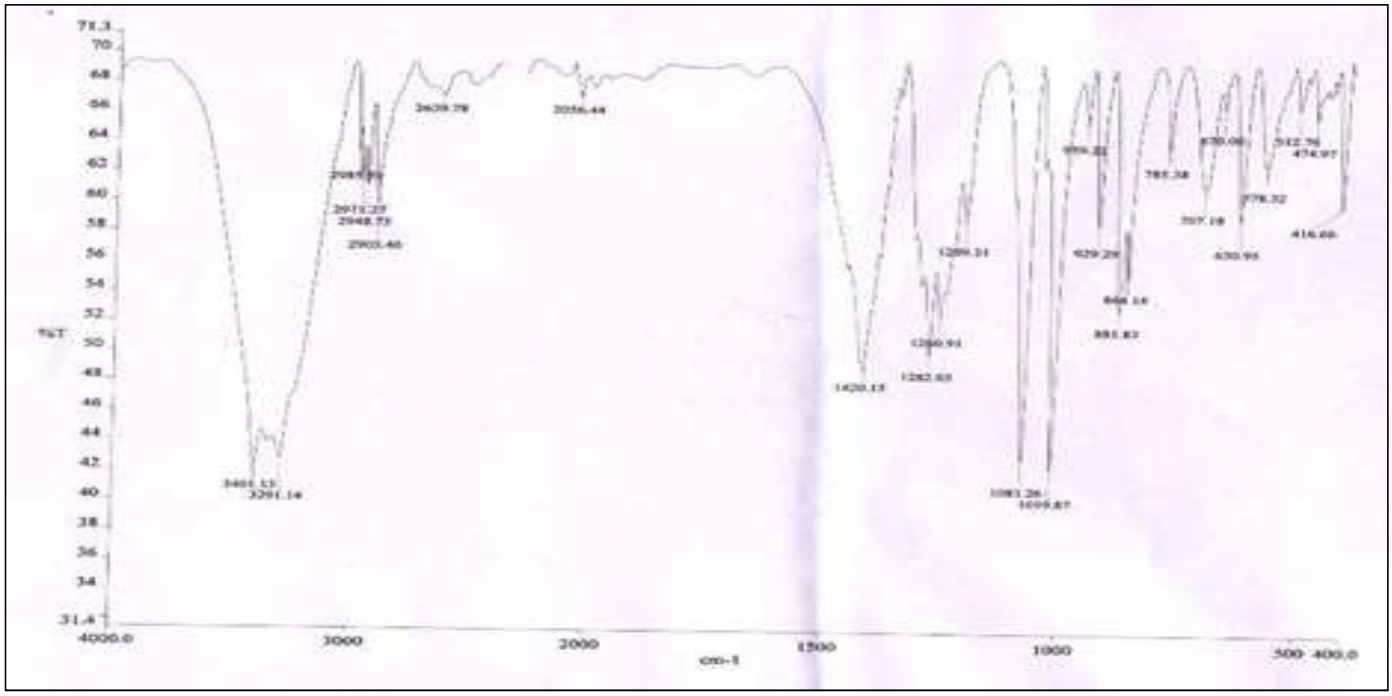

Figure No.2: FT-IR spectra of pure Mannitol

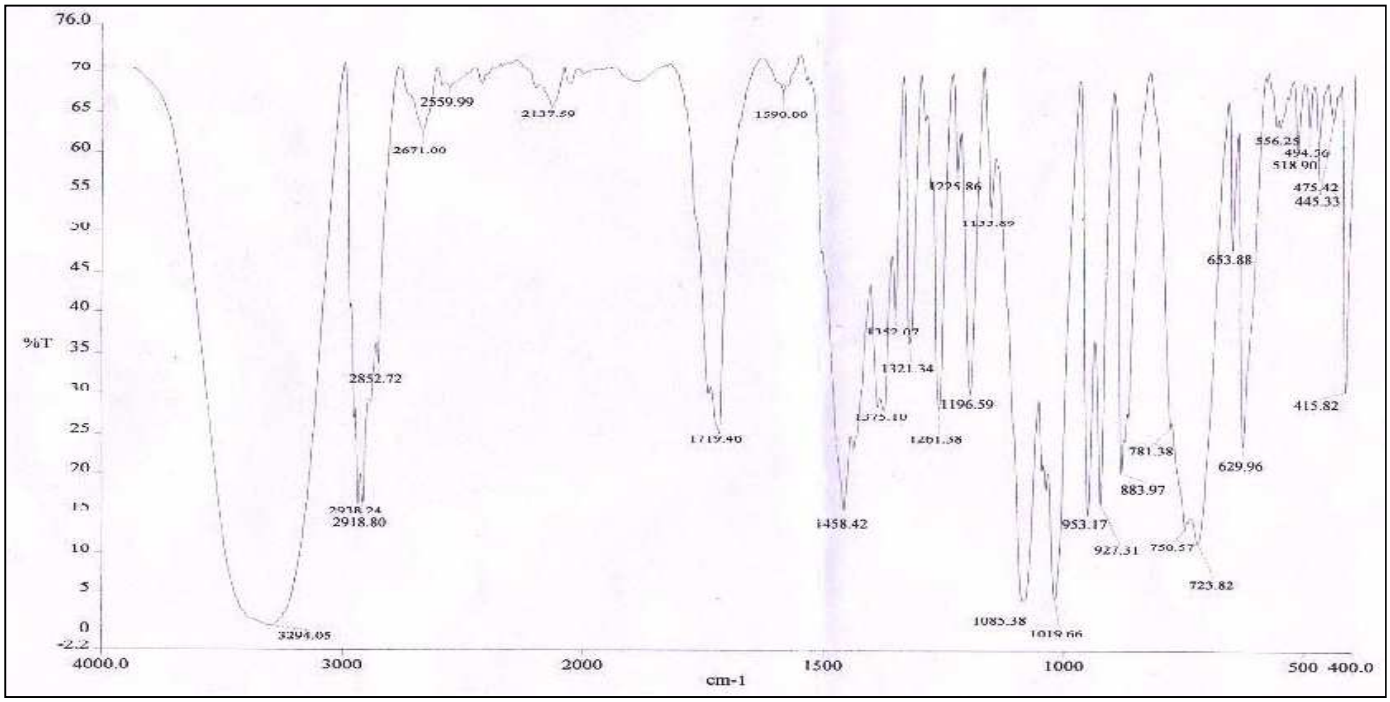

Figure No.3: FT-IR spectra of pure Aceclofenac and Mannitol

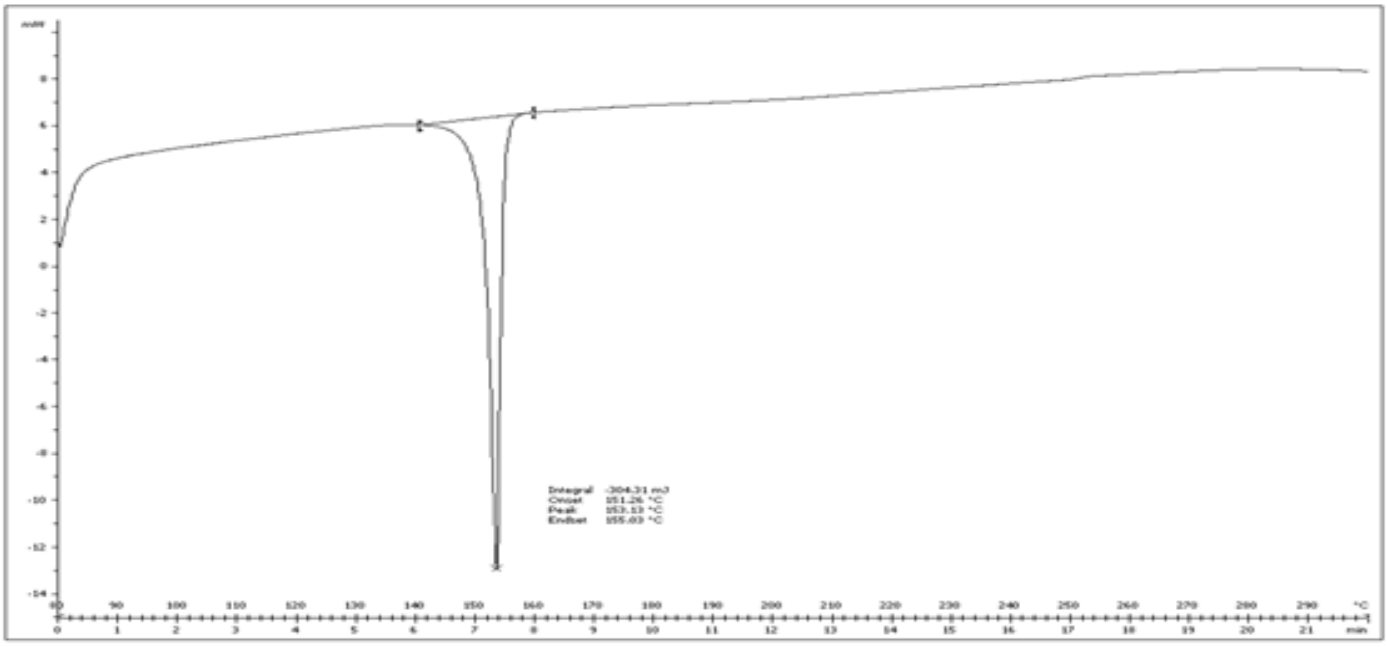

Figure No.4: DTA Pattern of pure Aceclofenac

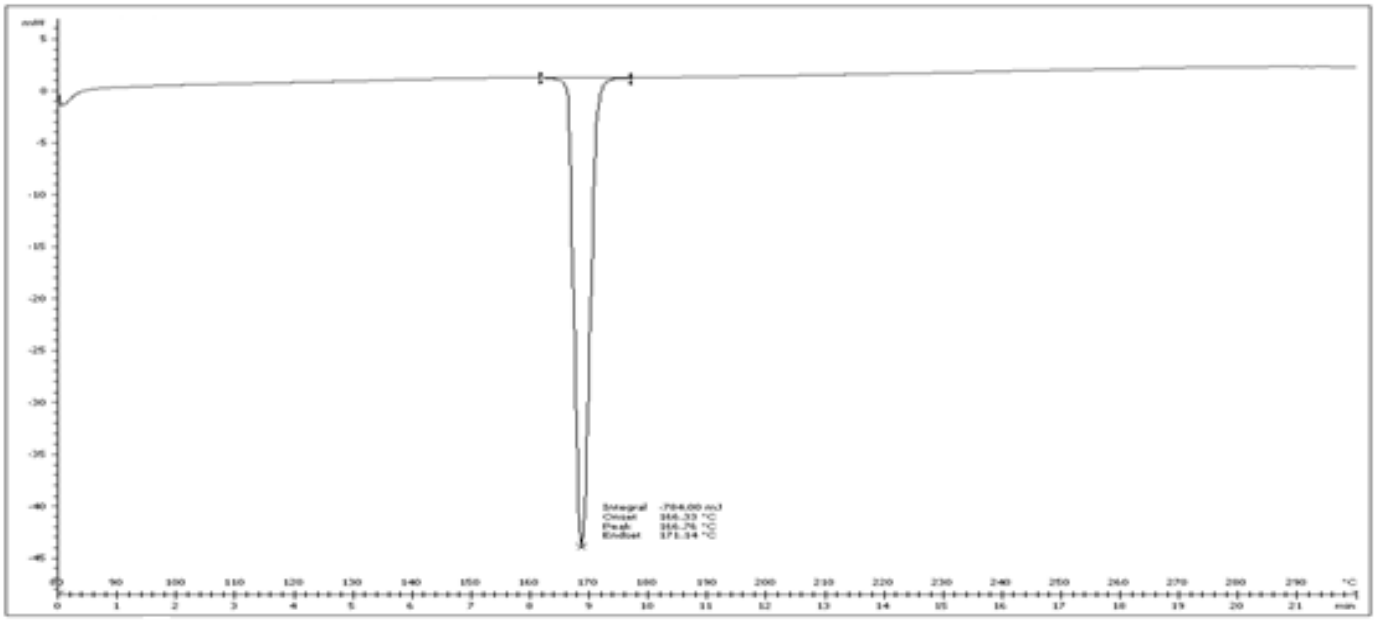

Figure No.5: DTA Pattern of pure Mannitol

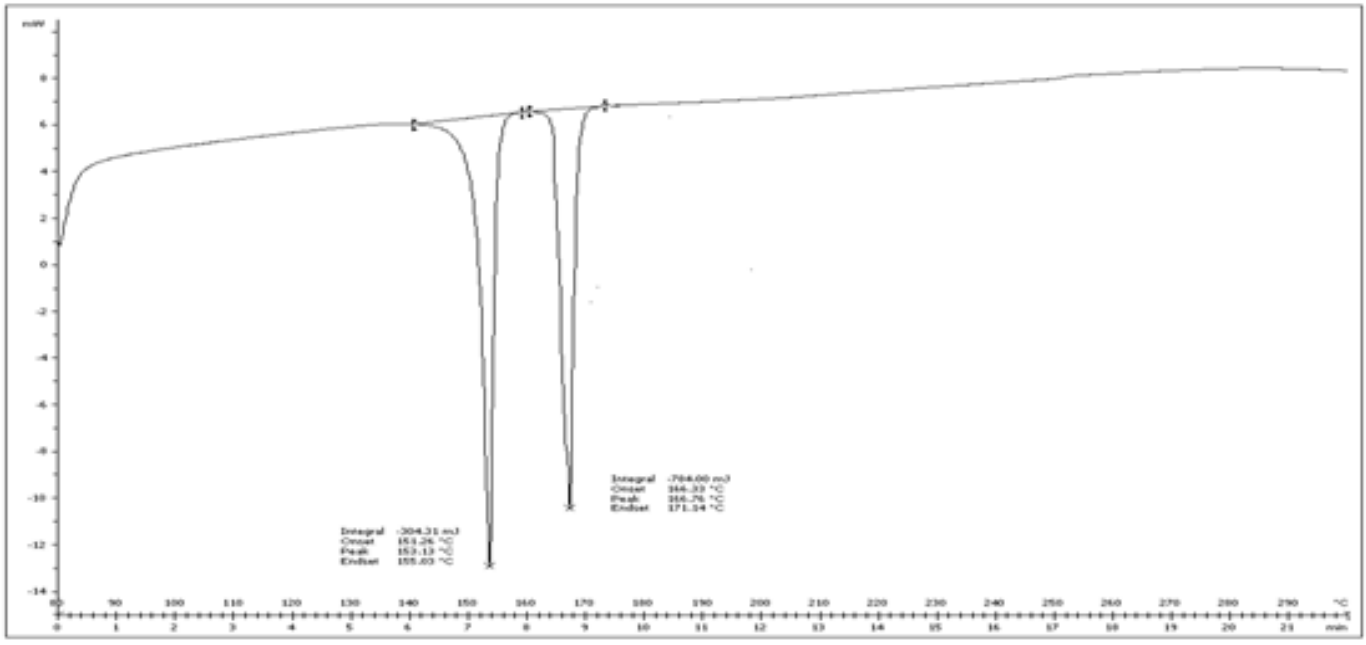

Figure No.6: DTA Pattern of pure Aceclofenac and Mannitol (1:4)

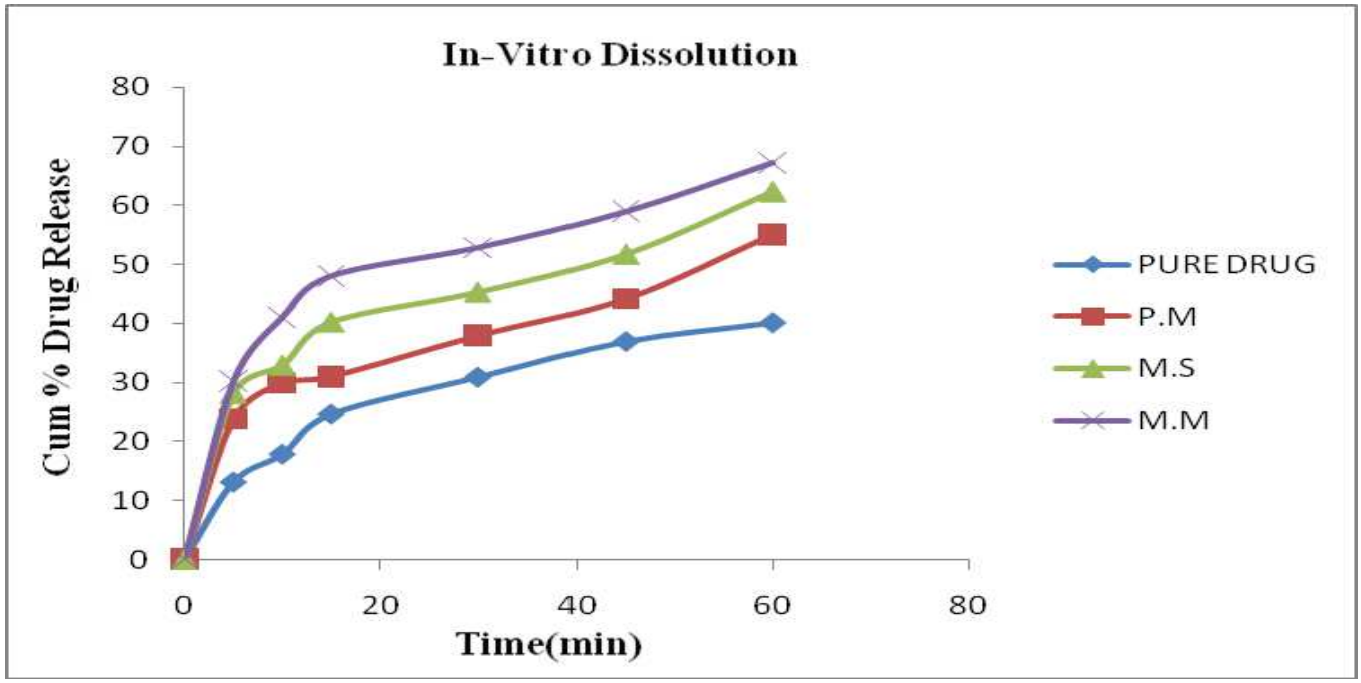

Figure No.7: Comparative dissolution profile of pure Aceclofenac and Aceclofenac: Mannitol (1:1)

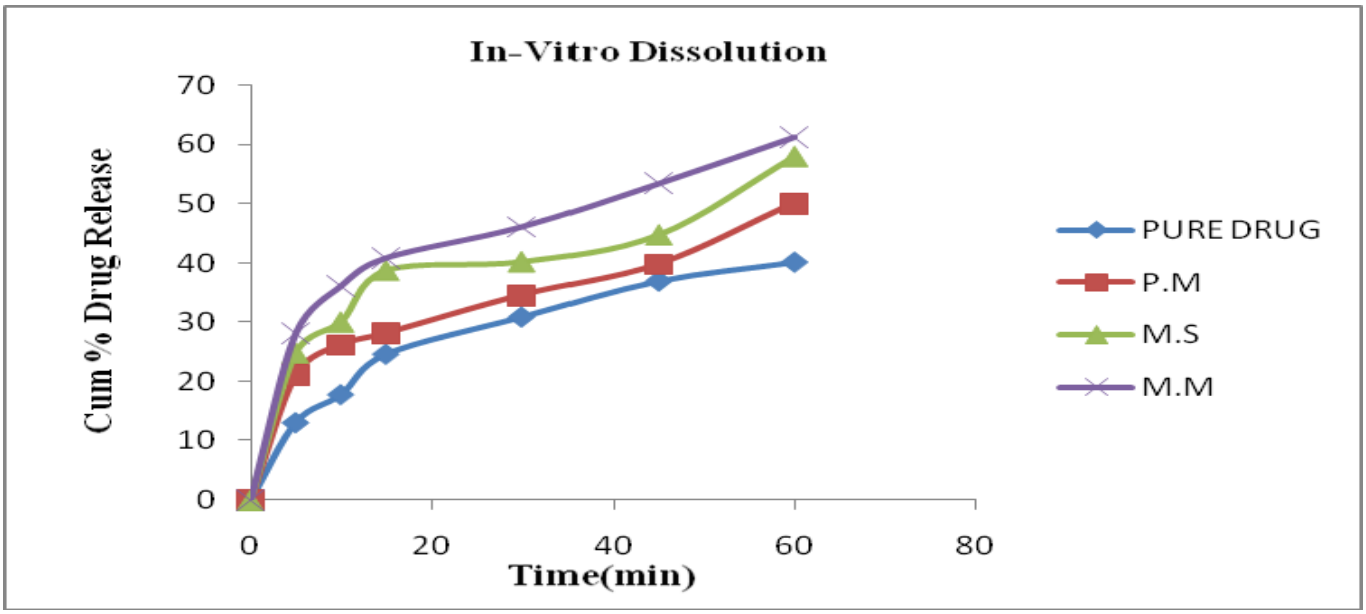

Figure No.8: Comparative dissolution profile of pure Aceclofenac and Aceclofenac: Mannitol (1:2)

Figure No.9: Comparative dissolution profile of pure Aceclofenac and Aceclofenac: Mannitol (1:3)

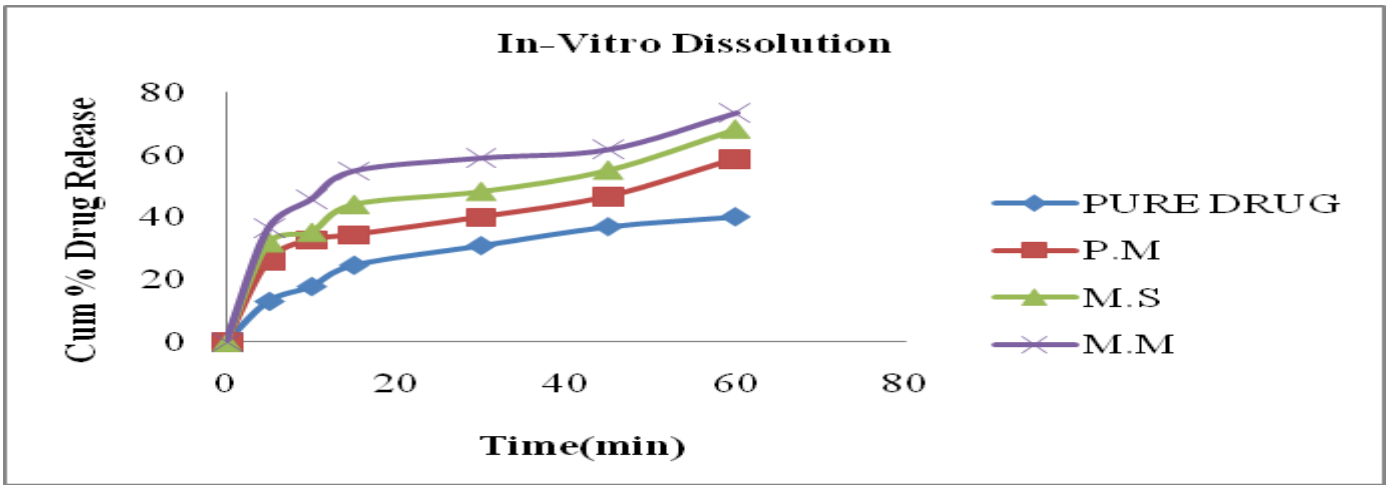

Figure No.10: Comparative dissolution profile of pure Aceclofenac and Aceclofenac: Mannitol (1:4)

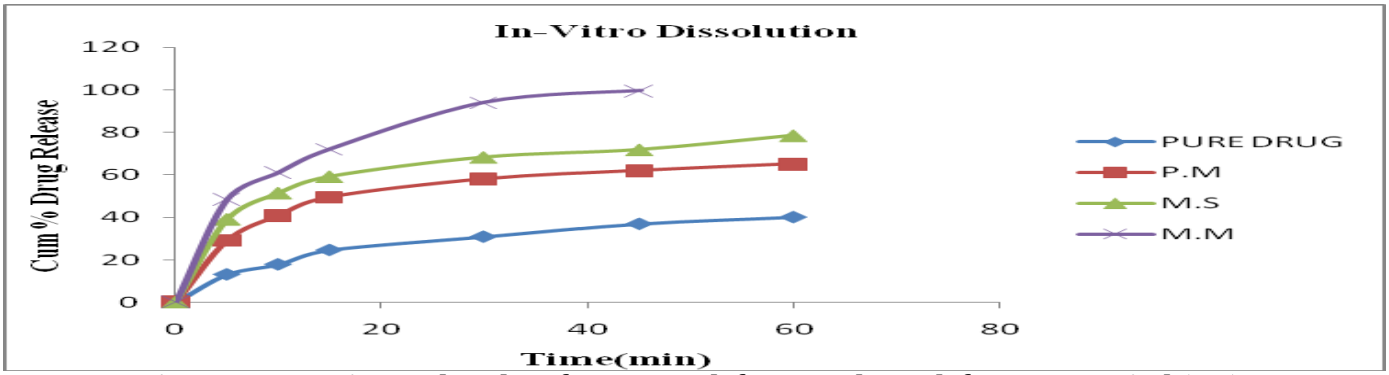

Figure No.11: First order plot of pure Aceclofenac and Aceclofenac: Mannitol (1:1)

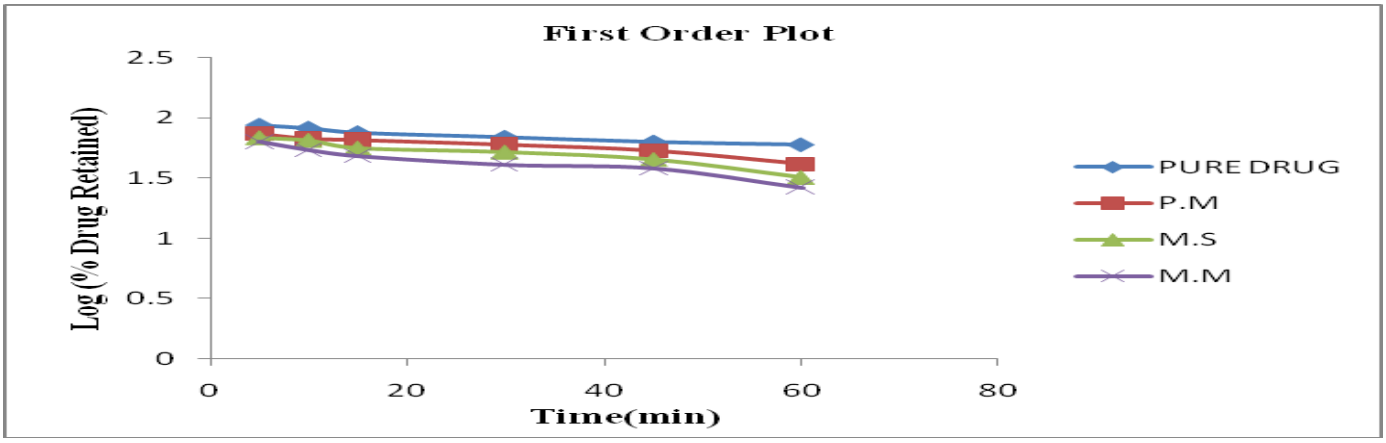

Figure No.12: First order plot of pure Aceclofenac and Aceclofenac: Mannitol (1:2)

Figure No.13: First order plot of pure Aceclofenac and Aceclofenac: Mannitol (1:3)

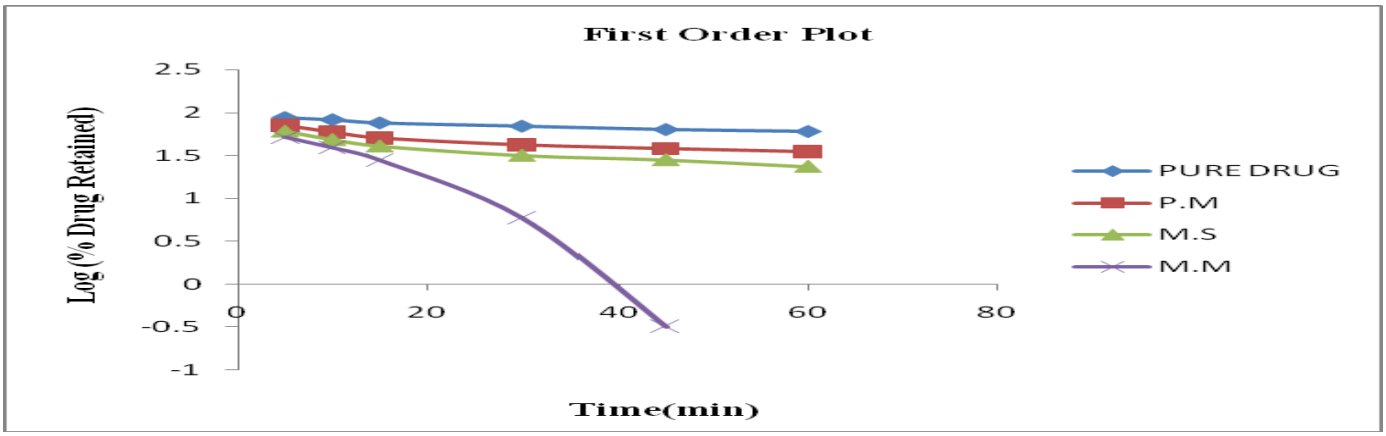

Figure No.14: First order plot of pure Aceclofenac and Aceclofenac: Mannitol (1:4)

CONCLUSION

The novel drug - carrier solid dispersion approach clearly indicates that such an approach can be extended to all fixed dose combination of insoluble/poorly soluble and water soluble drugs for improving dissolution and bioavailability of poorly soluble drugs. A detailed assay on the therapeutic integrity of the drugs is essential for viability of this novel approach for development of formulations with improved bioavailability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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