REPORT

Formulation and evaluation of suspensions: Mefenamic acid prodrugs

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Abstract: Gastrosparing novel prodrugs (MAM and MAT) synthesized consisted of mefenamic acid (MA) with menthol (M) and thymol (T). Structural characterizations of synthesized esters were done by Infra red spectroscopy (IR), proton nuclear magnetic resonance (^{1}HNMR), mass spectroscopy. After evaluation of pharmacological i.e. anti-inflammatory, analgesic and ulcerogenic activities, the preformulation studies were undertaken. Based on these a few formulation (suspensions) were designed and prepared. The formulated suspensions were evaluated for content uniformity, sedimentation volume, recovery studies, redispersibility, viscosity, pH, particle size, zeta potential, effect of temperature and *in-vitro* dissolution rate. All the above parameters were found to be within the limit these indicated that the synthesized esters are good candidate for liquid dosage form. Thus it can be concluded synthesized prodrugs can be formulated in suspension form.

Keywords: Mutual prodrug, mefenamic acid, suspensions, dissolution, preformulation.

INTRODUCTION

The suitable formulation for the synthesized drugs is always a challenge for the researchers. The compatibility of all the components including pharmaceutical active ingredients plays significant role in designing the formulation so always it is taken into consideration. The designed formulation should be such that onset and duration of drug action must not be altered with retention of the desired action. The developed formulation should be cost effective, stable and physiologically the active ingredients should be available on release. Drugs dispensed as suspensions for different reasons, but the most common is the poor aqueous solubility. Drug formulated as suspensions are more bioavailable than solid dosage form (Ansel and Popovish, 1995). Possible modification of the drug's bioavailability can be another advantage of this dosage form, delayed drug result in clinically useful plasma concentration of the drug (Radebaugh, 1990). The synthesized mutual prodrugs of mefenamic acid were taken to form suitable dosage form. The prodrugs were already reported as chemically stable and biolabile (Shah *et al.,* 2013). These prodrugs exhibited retention of anti-inflammatory and analgesic activities with significant reduced ulcerogenicity as compared to the mefenamic acid, So authors aims to explore preformulation studies and develop (Carstensen, 1990) suitable suspension formulations (eight) for synthesized prodrugs. The formulated suspensions are evaluated *in-vitro* for drug content, sedimentation volume, redispersibility, viscosity, pH, particle size, zeta potential and dissolution rate (Crick and Kendrew, 1987), (Strum *et al*, 1978), Marty and Wersey, 1975) and (Hashem and El-Said, 1987).

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MATERIALS AND METHODS

Brookfield viscometer (Model LV, DV-E), Zetameter, Malvern Instruments Ltd., pH meter, Dissolution apparatus USP II, Cyberlab HPLC system, USA, with column HISEIDO C18 column, MG 5µm, size-4.6 mm ID X 250 mm, consist of 7725i (Rheodyne) injection system, USA. The Analytical make, UK UV/Visible spectrophotometer was used for experiment. M/S Zydus Cadila, Ahmedabad, Gujrat, India gifted Mefenamic acid as sample. The analytical/spectroscopic/HPLC grade reagents and solvents used in the experiment.

Development of analytical method for estimation of prodrugs

The high performance liquid chromatography (HPLC) method developed for the estimation of prodrugs (MAM and MAT). The mobile phase used was methanol: acetonitrile (95: 5) at 279 nm with flow rate of 1 mL/min.

Standard stock solution

Accurately weighed quantity of prodrugs MAM/MAT (10 mg) were transferred to 10mL volumetric flasks. The prodrugs dissolved in methanol and volume was made up to the mark. The solution was diluted suitably with mobile phase to obtain the standard stock solution containing 10 µg/mL.

Development of procedure

The objective of this study was to develop suitable method by which the concentration of prodrugs can be

estimated under isocratic conditions. The mobile phase used was methanol: acetonitrile (95: 5). The flow rate was raised to 1 mL/min gradually. Once the pump achieved the stability, the sample (20µL) was injected through the rheodyne injector. The retention time of prodrugs MAM and MAT were recorded 4.06 and 7.57 minutes respectively at 279 nm. The chromatograms of prodrug MAM and MAT are given in figs. 1-2. The peak areas of the chromatograms noted.

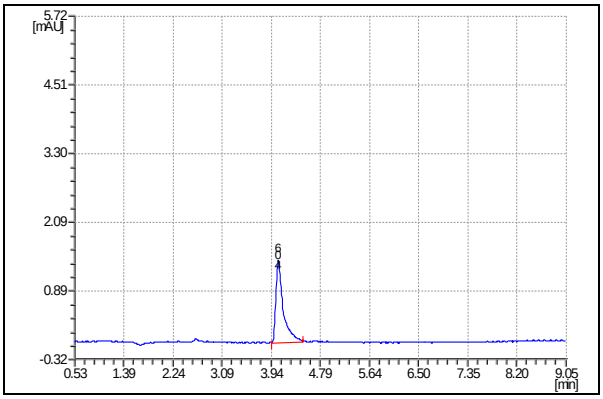


Fig. 1: Chromatogram of prodrug (MAM)

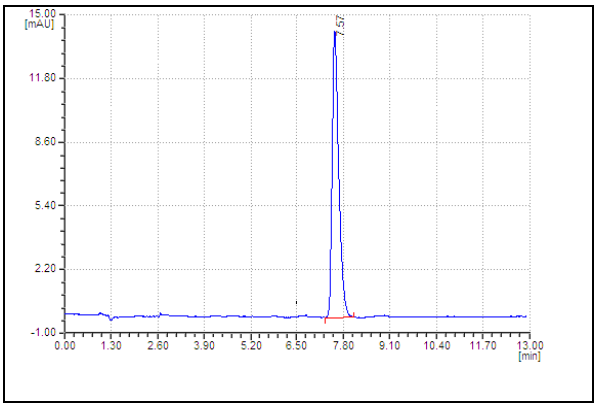


Fig. 2: Chromatogram of prodrug (MAT)

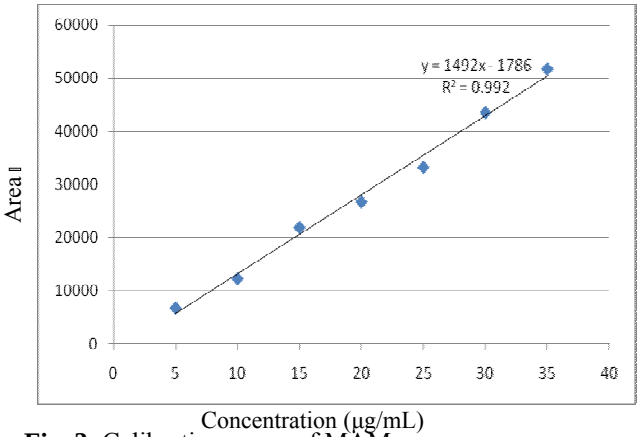


Fig. 3: Calibration curve of MAM

Calibration curve of prodrugs

The stock solution was prepared diluted suitably to obtain 1-10 µg/mL solutions of prodrugs. Then peak area versus concentration plotted in figs 3 and 4.

Preformulation studies of synthesized mutual prodrugs

Preformulation is defined as an investigation of physical and chemical properties of a drug substance alone and combined with excipients. It's a physicochemical characterization of the solid and solution properties of compounds. The definition of preformulation proposed by Akers 1976 was 'preformulation testing encompasses all studies enacted on a new drug compound in order to produce useful information for subsequent formulation of a stable and biopharmaceutically suitable drug dosage form. Objectives of preformulation studies are, to establish the necessary physicochemical parameters of a new drug substance, to develop the stable and bioavailable dosage forms, to establish kinetic rate profile, to establish its compatibility with common excipients. Preformulation studies done in order to determine the optimum conditions for the physical and chemical stability of prodrugs in dosage forms.

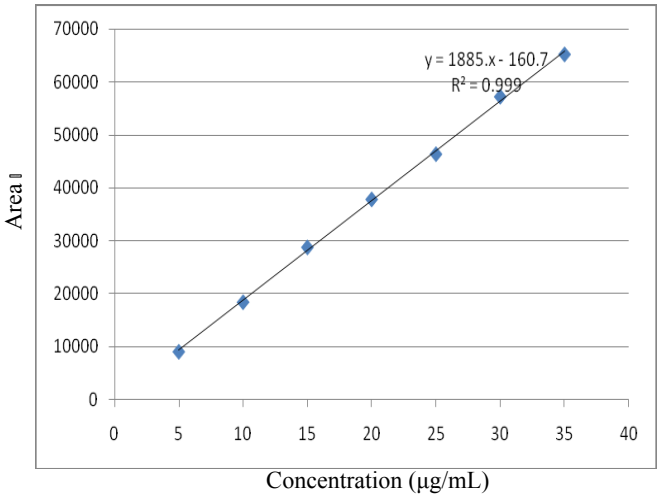


Fig. 4: Calibration curve of MAT

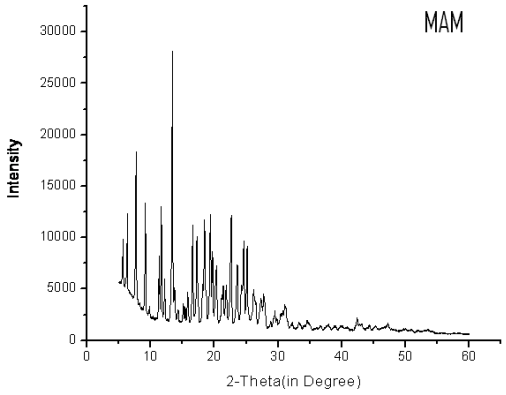


Fig. 5: XRD graph of prodrug (MAM)

Organoleptic properties and Particle size determination

The organoleptic properties colour, odour and taste of synthesized prodrugs examined and observations were

recorded. Prodrugs were found to have off white in colour, odourless and tasteless. Stage micrometer used to calculate out particle size of prodrugs. The powder of prodrug suspended in propylene glycol and a drop of suspension placed on a glass slide. Two hundred particles were sized and mean of particles were reported. Mean particle sizes (µm) for prodrug MAM and MAT were 21.12 and 24.32 respectively.

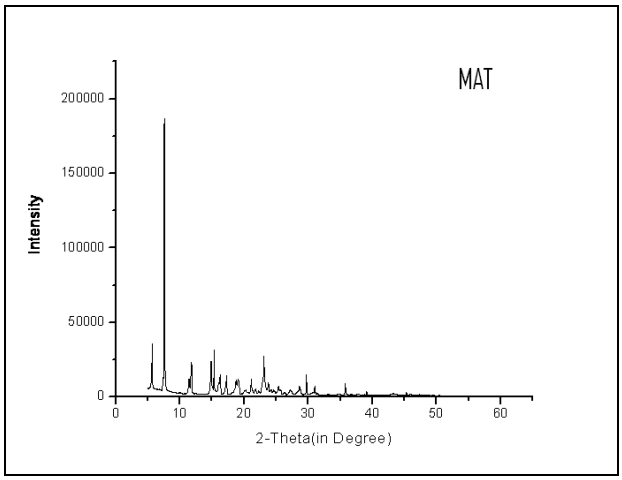


Fig. 6: XRD graph of prodrug (MAT)

Crystal Properties

X-ray diffraction study of prodrugs was performed by X-ray generator, New D8 Advance XRD (Bruker), under following conditions λ=1.542 °A (CuKα), 2θ=2π to 90π. The prodrug powder placed in sample holder and exposed to CuKα radiation for 36 min scan and X-ray diffraction pattern was obtained. The X-ray diffraction patterns of prodrugs are depicted in figs. 5 and 6.

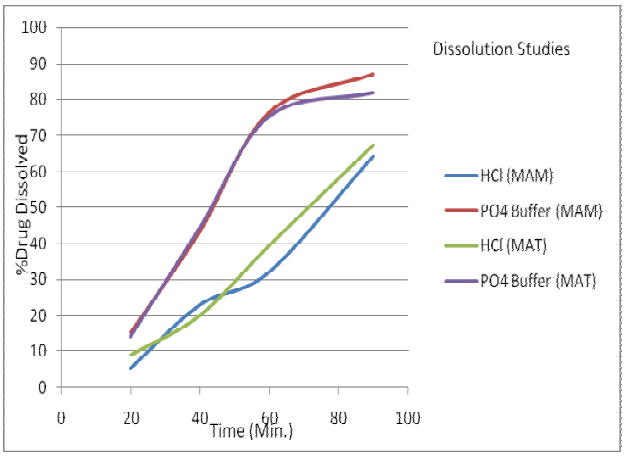


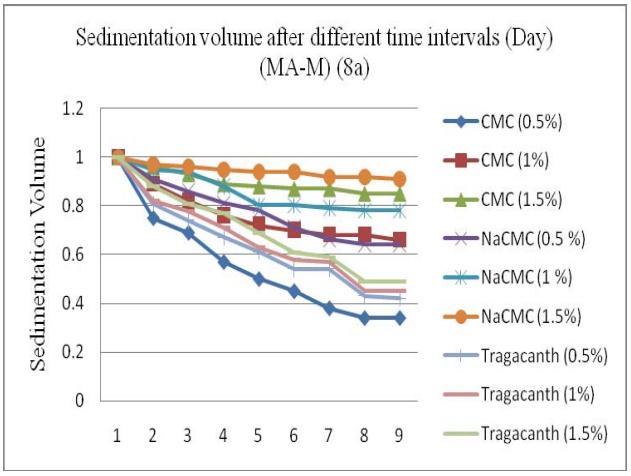
Fig. 7: Dissolution Studies of prodrugs

Solubility

The synthesized prodrugs found to be freely soluble in 0.1 N sodium hydroxide at 37±1 °C. The drug and prodrugs were remained insoluble in water and in 0.1 N Hydrochloric acid. The synthesized prodrugs had moderate to high solubility in various solvents such as methanol, ethanol, chloroform, dichloromethane and benzene which indicate lipophilic behavior of the compounds.

Partition coefficient

The n-octonol/phosphate buffer (pH 7.4) used to determine the partition coefficients of prodrugs. Drugs were taken in n-octanol (10 mL) and equal volumes of phosphate buffer in separating funnel. The separating funnel were thoroughly shaken for 2 h at room temperature and left for 1 h. The aqueous phases were extracted with chloroform three times. Thereafter, the respective phases were analyzed by developed HPLC assay. The value of partition coefficients of MAM and MAT were found to be 4.98 and 5.45 respectively.



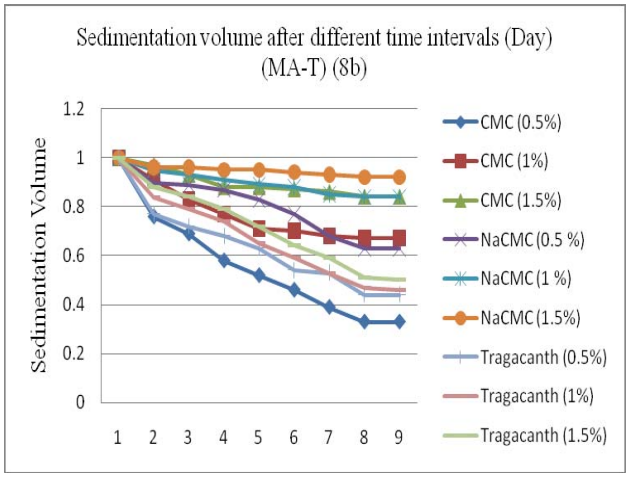


Fig. 8: Graph for sedimentation volume of suspensions containing different concentration of suspending agents during selection

Powder flow properties

Angle of repose

The powder funnel was fixed using a retort stand, so that bottom of orifice is 10 cm above the table surface. The funnel was filled with prodrugs. The contents were then allowed to pour on a graph paper placed on the table to

form a heap. The diameter (d) and height (h) of heap was measured. The experiment was repeated three times.
Angle of repose (θ) calculated using equation:
$\theta = \tan^{-1} 2h/d$
Carr's compressibility index
It is calculated by the following formula.
Carr's compressibility index=1-poured density/tapped density X 100
Angle of repose and Carr's compressibility index was found to be 22.36, 28.24 and 11.26, 19.29 for MAM and MAT respectively.

Dissolution Studies
Dissolution studies of prodrugs were carried out in 0.1N hydrochloric acid and phosphate buffer (pH 7.4) as dissolution media separately. The USP dissolution apparatus II used. Prodrugs (100mg) placed in 1L of dissolution media at 100 rpm (37±0.5 ºC). The aliquots 5 mL withdrawn at each time interval and replaced with fresh dissolution medium of equal volume. The samples were filtered and extracted with 5 X 3mL chloroform. The extracts were combined and evaporated. The residues were dissolved in methanol further concentration recorded by HPLC (fig. 7).

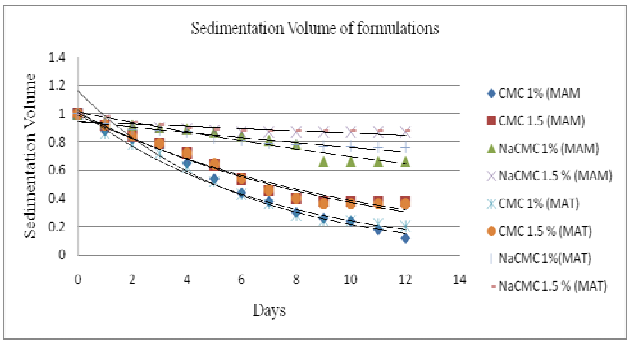


Fig. 9: Graph for sedimentation volume of formulations (suspensions) containing different concentration of suspending agents

Influence of pH on stability
The influence of pH on degradation of prodrugs was determined in phosphate buffer of pH range from 3.6 to 7.2. The phosphate buffer of pH 3.6, 4.0, 5.0, 6.0 and 7.2 were prepared. Accurately weighed prodrugs 10 mg were triturated in a glass mortar pestle with respective buffer solution and final volume was made upto 10 mL with same buffer solution. The vials were kept and after a day, daily for 8 days 1mL of sample were withdrawn and extracted with 5 X 3mL of chloroform. The extracts were combined and evaporated. The residues were dissolved in methanol further concentration recorded by HPLC (table 1).

Influence of composition of different vehicles
The proper selection of vehicle was carried experimentally. The aim of the experiment was to find out the vehicle in which the drug degradation is minimum. Accurately weighed prodrug (10 mg) was triturated in a mortar about 2mL of vehicle and final volume was made to 10mL with same vehicle. Kept in vials and after a day, daily for 8 days 1mL of sample were withdrawn and extracted with 5 X 3mL of chloroform. The extracts were combined and evaporated. The residues were dissolved in methanol further concentration recorded by HPLC (table 2).

Selection of suspending agent
Suspensions were prepared with methylcellulose (0.5, 1.0 and 1.5%), Sod. CMC (0.5, 1.0 and 1.5%) and tragacanth (0.5, 1.0 and 1.5%). The concentration of wetting agent i.e. tween 80 was kept 0.1% w/v. Ten mL of each suspension was taken and its sedimentation volume was noted after every 24 h for 9 days. Formula of suspensions containing different concentration of suspending agents given in Figure 8a and 8b (Venkateshwarlu *et al.,* 1990).

Selection of wetting agent
Accurately weighed prodrug (100 mg) was shaken with 5 ml of distilled water in a test tube. It was observed that prodrug was floating on the surface of water. Therefore aqueous solutions (0.1% w/v) of surfactants possessing HLB 7 to 9 such as Tween 40, 60, 80 and propylene glycol were prepared. Wetting agent (0.5mL) was placed on one end of clean glass slide on the other end of which was placed 20 mg of prodrug powder. The time taken by wetting solution to penetrate the prodrug powder was noted. On the basis of above study, Tween 80 (0.1% w/v) was found to be best wetting agent amongst the other used (Iermpio and Zatz, 1980).

Preparation of suspensions of prodrugs
The suspension excipients were selected on the basis of review of literature and preformulation studies. The four formulae of each mutual prodrug (total 08 formulations were designed) (table 3). The weighed quantities of prodrugs were wetted by trituration with aqueous solution of wetting agent. Glycerin was added by trituration to form smooth paste. Now water soluble ingredients (sodium citrate, sodium benzoate) were dissolved in water and added slowly and triturated. Potassium chloride dissolved in water added with trituration. Thereafter aqueous solution of suspending agent and syrup was added to above mixture with trituration. Then flavor was added and mixed. The suspension so formed transferred to a measuring cylinder and volume was made to 100 mL.

Evaluation of formulated suspensions of prodrugs
Content uniformity
Each product was taken in three different bottles. A sample 1mL was taken from first bottle at the top, from second bottle at the middle and from a third bottle at the bottom. The prodrug content in samples so withdrawn was extracted by shaking with 5 X 3mL of chloroform. The extracts were combined, evaporated and estimated chromatographically.

Table 1: Percent residual of MA-M at various time intervals in different pH

Time (days)	% Residual of MA-M at various time intervals in different pH					% Residual of MA-T at various time intervals in different pH				
	3.6	4.0	5.0	6.0	7.2	3.6	4.0	5.0	6.0	7.2
0	100	100	100	100	100	100	100	100	100	100
2	93.4	94.6	97.4	92.8	86.4	91.4	96.3	91.0	88.0	86.0
4	87.6	87.4	93.6	85.5	74.0	89.9	93.4	87.4	81.4	75.3
6	81.3	83.6	91.6	80.8	69.8	80.4	89.0	82.0	74.8	66.8
8	77.1	79.4	90.5	76.0	63.7	76.4	87.6	77.6	70.2	61.6

Table 2: Percent residual of MA-M at various time intervals in different vehicles

Time (days)	% Residual of MA-M at various time intervals in different vehicles					% Residual of MA-T at various time intervals in different vehicles				
	I	II	III	IV	V	I	II	III	IV	V
0	100	100	100	100	100	100	100	100	100	100
2	93.6	91.6	91.4	98.3	97.3	96.4	92.7	91.0	98.4	97.3
4	91.2	84.6	81.2	94.2	93.2	93.1	84.8	81.8	91.6	92.2
6	87.1	76.1	75.4	91.8	89.9	89.4	78.0	77.4	89.1	90.5
8	84.6	70.6	69.0	89.4	88.2	84.6	72.0	71.0	88.5	88.8

I=Simple syrup, II=Propylene glycol 10% w/v, III=Propylene glycol 20% w/v, IV=Glycerin solution 10% w/v, V=Glycerin solution 20% w/v

Sedimentation Volume

Suspensions (10mL) were filled in graduated cylinders of 10mL capacity. These cylinders were kept undisturbed and the reading was noted initially, then after 24 h for 15 days. The sedimentation volume was calculated (fig. 9).

Recovery studies

The recovery studies done by adding pure drug 10 mg to the each formulation then concentration calculated out. It was found to near 100%.

Table 3: Formulas for suspensions of prodrugs

Ingredients	% Of ingredients in formulations			
	I	II	III	IV
MA-M/ MA-T	2	2	2	2
Tween 80	0.1	0.1	0.1	0.1
KCl	0.003	0.003	0.003	0.003
Methyl Cellulose	1	1.5	-	-
Na CMC	-	-	1	1.5
Sodium citrate	2.3	2.3	2.3	2.3
Sodium benzoate	0.1	0.1	0.1	0.1
Glycerin	10	10	10	10
Syrup	50	50	50	50
Flavour	1	1	1	1
Water q.s.	100	100	100	100

Redispersibility

Suspensions without flocculating agent had poor redispersibility while suspensions having flocculating agent (potassium chloride) had good redispersibility. The redispersibility was calculated by placing suspensions 10 mL in measuring cylinder and stored for 10 days. The measuring cylinder was tilted to 90º until the sediment dispersed uniformly. However the time required for complete dispersion was recorded. The formulation IV was having excellent redispersibilty.

Zeta potential

The zeta potential of formulated suspension was measured by taking one mL of the suspension. The one mL of suspension was further diluted to 50 mL with distilled water and filled in the cleaned capillary tube (provided with the instrument) with a pipette and measurements were done.

Effect of temperature

The pH of formulated suspensions were almost remain constant after storage of 3 weeks at RT, while at higher temperature slight deviation is noted.

Particle size

Determined by stage micrometer and compared with formulations kept at higher temperature (50 ºC). It was found that at higher temperature the particle size got increased this gives the idea that formulated suspensions are prone to crystal growth if kept at higher temperature.

In vitro dissolution studies

Dissolution studies were carried out in 1L, 0.1 N HCl as reported earlier for prodrugs.

RESULT

In order to optimize liquid (suspensions) formulations of prodrugs of mefenamic acid preformulation studies were performed. Organoleptic properties and particle size of

Table 4: Evaluation Parameters of suspensions

F. No.	Average Particle Size (µm)	Viscosity (cp)*	pH	Zeta Potential (mV) (-ve)	Content Uniformity (%) *	Redispersibility* (sec.)	Dissolution* ($t_{50\%}$)	Dissolution rate (%/min)	Recovery Studies (%) *
I	12.2	67	4.85	32.4	97.880±0.658	72	39.143	1.27	97.101±0.352
II	14.3	144	4.72	30.8	97.910±1.004	62	35.869	1.508	95.388±0.779
III	10.4	40	4.68	28.7	97.680±1.228	61	35.647	1.496	94.566±0.348
IV	10.2	42	4.88	31.4	97.740±1.127	40	34.514	1.543	97.433±0.183
V	14.2	74	5.12	16.8	97.430±0.730	65	41.762	1.285	94.388±3.298
VI	12.4	126	5.22	14.2	97.406±0.959	57	35.95	1.494	95.433±1.301
VII	10.6	27	5.02	15.4	97.746±1.262	48	35.624	1.461	96.133±0.961
VIII	10.2	30	4.98	14.6	97.293±1.040	35	35.176	1.499	97.311±0.652

*Average of three determination

prodrugs were determined. The desired particle size for oral suspension is 1-50µm (Bhargava and Nicolai, 1989). Therefore the synthesized prodrugs are good candidates for their formulation as suspensions. X-ray diffraction studies of prodrugs were performed by X-ray generator and graph showed that MAM and MAT produced diffraction patterns characteristics of crystalline powder. Flow properties of prodrugs were studied by determining angle of repose and Carr's index. The result showed their good flow properties. The result of solubility studies indicated that the prodrugs are poorly water soluble and highly soluble in organic solvents. The partition coefficient study said that the prodrugs will be absorbed better from stomach rather than intestine. The dissolution rate study indicated that prodrugs were slowly dissolved in 0.1 N hydrochloric acid while faster in phosphate buffer (pH 7.4). The dissolution of both prodrugs follow linear relationship between percent drug release versus time, indicative of zero order kinetics. The influence of pH on stability of synthesized prodrugs indicated that rate of degradation of prodrugs was increased with the increasing pH, this may be due to enhanced solubility of prodrugs, making more of the drug available for degradation. In the selection of vehicle, the rate of degradation of prodrug was studied in five commonly used vehicle compositions. The study showed maximum stability of prodrugs in 10% glycerin. This vehicle also acts as sweetening agent. In the selection of wetting agent, it was observed that the solution of Tween 80 (0.1% w/v) took less time to penetrate the powder (Falkiewicz, 1989). The suspension prepared with sodium carboxymethyl-cellulose and methyl cellulose showed maximum sedimentation volume as compared to other suspending agents. The synthesized formulations (suspensions) were evaluated (table 4). All the formulations were analyzed for the prodrug content, which was found in the range of 97.293-97.910 percent. This indicates formulation had excellent content uniformity. Formulation VI and VIII containing 1.5% sodium carboxymethylcellulose were shown maximum sedimentation volume and dispersion as compared to other formulation. The formulations containing sodium carboxymethylcellulose as a suspending agent showed less viscosity than the formulations containing carboxymethylcellulose as suspending agent. The microscopic examinations of formulated suspensions of the prodrugs showed no change in particle size. The observations revealed that the formulated suspensions of prodrugs are not prone to crystal growth. The zeta potential of all the formulated suspensions were found in the range of 14.2 to 31.4 mV, which is the usual range required for flocculation of suspended drug particles. The *in vitro* dissolution studies of formulated suspension showed that all formulations followed zero order release kinetics. The formulation IV was found to exhibit faster dissolution rate as compared to its other formulation and t 50% was found to be 34.51.

DISCUSSION

All the prodrugs were tasteless and odorless. The colors of the prodrugs were dark yellow to off white.The particle sizes were found to be 21.12 and 24.32 µm for MAM and MAT respectively. Thus all the synthesized compounds had optimum range of particles which is required for suspension i.e. 1-50 µm as given in literature. X-ray diffraction studies gave specific graph produced diffraction patterns characteristics of crystalline powder. Solubility studies showed that only MA was found highly soluble in 0.1 N sodium hydroxide. This attributed to the presence of free –COOH group. The synthesized prodrugs showed moderate to high solubility in various organic solvents, which indicate lipophilic characterstic of the compounds. In the present studies, all the compounds showed the value of log P in the range of 4.5 to 5.5 thus it can be expected that the synthesized compounds would be suitably absorbed from GIT. All the synthesized compounds showed good flow properties as evidenced by their data. The influence of pH on stability of synthesized prodrugs was studied in phosphate buffer (pH 3.6 to 7.2). This study indicated that rate of degradation of prodrugs increased with the increasing pH. This may be due to

enhanced solubility of prodrugs, making more of the drug available for degradation. For the selection of vehicle for formulation, the rate of degradation of prodrug was studied in five commonly used vehicles.Maximum stability of prodrugs was found to be in 10 % glycerin. Incidently this vehicle has one added advantage of being sweet in taste. Out of the wetting agents tried i.e. Tween 40, 60, 80 and propylene glucol (0.1 % v/v), the Tween 80 was found to be most suitable. The suspension prepared with sodium carboxymethylcellulose and methyl cellulose showed maximum sedimentation volume as compared to Tragacanth. The 1 and 1.5 % of CMC and Sod. CMC were selected as suspending agent. Preformulation studies undertaken and gave an indication that the synthesized prodrugs are a good candidate for formulation. All the formulations were analyzed for the drug content, which was found in the range. The test indicated the uniformity of drug content. The result of recovery studies showed near about cent percent recovery. In the sedimentation volume studies the observation suggests the stability of the suspension. This may be attributed to the greater concentration of suspending agent (1.5 % w/v). Then the redispersibility test was performed formulation IV had excellent dispersion (40 sec.) as compared to other formulations. The measured zeta potential of all the formulated suspensions was found to be within the limit of 25 mV (+ve or –ve) as specified in literature. During *in vitro* dissolution studies all the formulations followed zero order release kinetics. It was found that at higher temperature the particle size got increased this gives the idea that formulated suspensions are prone to crystal growth if kept at higher temperature. Thus it can be said that out of eight formulations, formulation IV had good dissolution rate 1.543 % min^{-1} and its $t_{50\%}$ was found to be 34.51 min.

CONCLUCSION

The pre synthesized prodrugs which are safer NSAIDs than standard are good candidate for suspension formulation. The side effects with mefenamic acid are gastric erosion, irritation, erosion of gastro duodenal mucosa and bleeding. However, if this drug is given in conjugation with thymol and menthol are viewed as good therapeutic agents for treating free radical mediated diseases like NSAID induced peptic ulcers and lowers the side effects of standard drug. Hence, in the present work conjugates were taken. Among eight formulations the IV formulation was found to be best. This work opens the field for further preclinical and clinical studies, development of other formulations for optimum drug delivery system.

ACKNOWLEDGMENT

One of the author's Mr. Kamal Shah thankful to GLA University, Institute of Pharmaceutical Research, Mathura UP, India for providing the research facilities to carry out this work, The authors also thanks to Cadila Healthcare Ltd. Ahmedabad-380015 Gujarat, India for providing the gift sample of Mefenamic acid. The author also thankful to UGC-DAE Consortium for Scientific Research, INDORE-CENTRE (MP) for providing X-ray study.

REFERENCES

Ansel HC and Popovish NK (1995). *In*: Pharmaceutical dosage forms and drug delivery system, 6th Edn. BI Waverly Pvt. Ltd., New Delhi, pp. 253-254.

Bhargava HN and Nicolai DW (1989) *In*: Lieberman, HA, Rieger MM and Banker GS. (Eds.) Pharmaceutical dosage forms: Disperse systems, Vol. 2, Marchel dekker, Inc., New York and Basel, pp. 275-279.

Carstensen JT (1990) *In*: Banker GS and Rhodes CT. (eds.) Modern Pharmaceutics, 2nd edn. Marcel dekker Inc., New York and Basel, p. 239.

Crick FHC and Kendrew JC (1987) *In*: Kittel C. Introduction to Solid-State Physics, 5th edn. Wiley Eastern Ltd., New Delhi, pp. 37-61.

Falkiewicz MJ (1989). *In*: Lieberman HA, Rieger MM and Banker GS (Eds.). Pharmaceutical dosage forms: Disperse systems, Vol. 1, Marchel Dekker, Inc., New York and Basel, pp. 26-30.

Hashem F and El-Said Y (1987). Effect of suspending agents on the characteristics of some anti-inflammatory suspensions. *Pharmazie.,* **42**: 732-735.

I'ermpio JS and Zatz JL (1980). Flocculation effect of xanthan gum in pharmaceutical suspensions. *J. Pharrn. Sci.,* **69**: 1209-1214.

Marty JJ and Wersey JA (1975). Apparatus for measuring *in vitro* availability of iquid oral preparations. *J. Pharm. Pharmacol.,* **27**: 437-438.

Radebaugh GW (1990), *In*: Gennaro AR (eds.) Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, p.147.

Shah K, Shrivastava SK and Mishra P (2013). Evaluation of mefenamic acid mutual prodrugs. *Med. Chem. Res.,* **22**: 70-77.

Strum JD, Colaizzi JL, Goehl TJ, Jaffe JM, Pitlick WH, Shah VP and Poust RI (1978). Bioavailability of sulfonamide suspensions I: Dissolution profiles of sufamethizole using paddle method. *J. Pham. Sci.,* **67**: 1399-1402.

Venkateshwarlu G, Rambu D, Ramesh BR and Sarveswar Rao VV (1990). Dissolution kinetics of rifampicin aqueous suspension. *Indian Drugs,* **28**: 8-12.