DESIGN AND ASSESSMENT OF COLON SPECIFIC DRUG DELIVERY OF MEFENAMIC ACID USING MODIFIED PULSINCAP TECHNIQUE AND HUPU GUM

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ABSTRACT

The aspiration of present work is to design a colon specific drug delivery of mefenamic acid (MA) by using modified pulsincap technique and hupu gum as hydrogel. Mefenamic acid being poorly water soluble drug, solubility has been increased by solid dispersion technique using natural gums such as guar gum (GG), hupu gum (HG) and xanthan gum (XG). Solid dispersions were prepared by kneading method at different weight ratios of 1:1, 1:2 and 1:3 of MA and selected polymers. Saturation solubility, pH dependent solubility, phase solubility and dissolution studies were conducted**.** The optimized solid dispersions have been used for the formulation of pulsincaps. Bodies were made insoluble by formaldehyde treatment. Solid dispersions of mefenamic acid were filled in the bodies. Hupu gum (HG) was used as plug. Sealing of body and cap were done using ethyl cellulose. Ethyl cellulose coating was employed to ensure the colon targeting of pulsincaps. % drug release of MA pulsincaps prepared with MA and solid dispersions of MA-GG, MA-HG and MA-XG was found to be 41.25, 91.44, 93.87and 88.4 respectively. The studies have clearly indicated that mefenamic acid in pulsincap formulations were very effective to deliver the drug specifically to colon.

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INTRODUCTION

Site specific drug delivery systems offer several advantages over the traditional drug therapies and due to this, a great deal of research has been carried out on these systems during the last few decades. The colon, as a site for drug delivery, offers distinct advantages like longer transit time,[1] relatively low proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers. Successful colonic drug delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. Several approaches have been developed for targeted colonic drug delivery. Most of them utilize the physiological properties of the GIT and colon such as pH of GIT, transit time of small intestine, luminal pressure of the colon, and the presence of microbial flora localized in the colon.[2]

Chronotherapy is either the timed delivery of medications according to biological rhythm in order to minimize dose-limiting adverse events or the delivery of medications in synchrony with endogenous biological rhythms associated with the pathophysiology of disease states to optimize treatment outcomes. The first chronotherapy to be widely applied in clinical practice was introduced in 1960s.[3] In order to meet the chronopharmaceutical demands, there is a need for designing dosage forms to elicit a programmed liberation of drugs after lag phases that commence upon administration[4, 5] .Such a release manner is commonly referred as pulsatile and/or delayed delivery. Pulsincap® is a patented preparation developed by R. P. Scherer International Corporation, Michigan, US, consisting of a hardened capsule body filled with basic drug mixture and sealed with hydrogel plug[6]. When this capsule comes in contact with the dissolution fluid, it swells; and after a lag time, the plug pushes itself out of the capsule and thereby the drug will be released quickly. Pulsincap® was studied in human volunteers and was reported to be well tolerated [7, 8].

Mefenamic acid (MA) is 2- [(2, 3- dimethylphenyl) amino] benzoic acid, belonging to the family of N-aryl anthranilic acid. It is one among the extensively used NSAIDs possessing mutually anti-inflammatory and analgesic activities. It is used in gentle to moderate pain including headache, dental pain, postoperative and postpartum pain, dysmenorrhoea, osteoarthritis. The chief side effects of MA are GIT disturbance, peptic ulceration and gastric bleeding. These gastroenteropathies usually result from the direct contact effect, which is due to the combination of local irritation produced by the free carboxylic group in the MA structure and by local blockage of prostaglandin biosynthesis in the GI tract[9]. In order to overcome these side effects, colon specific drug delivery system of MA has been investigated using modified pulsincap technique. The use of colon specific drug delivery system of MA using modified pulsincap technique has been investigated as an approach to reduce or suppress the GI toxicity due to the direct contact effect. Mefenamic acid belongs to class II category under Biopharmaceutical classification system i.e., it is inherently highly permeable through biological membranes, but exhibits low aqueous solubility. Rate of absorption and / or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids. To enhance the solubility of MA, solid dispersions were prepared by kneading method using guar gum, hupu gum and xanthan gum as carriers. The prepared solid dispersions were filled in the pulsincap ensuring colon targeting.

MATERIALS AND METHODS
Materials
Mefenamic acid was obtained as a gift sample from A-Z pharmaceuticals, Chennai; Guar Gum and Xanthan Gum was purchased from S.D. Fine Chem. Ltd., Mumbai; and Hupu Gum was bought from Sigma Aldrich, USA. All other chemicals used were of analytical grade.

Methods

Formulation of solid dispersions

Mefenamic acid and the various polymers [guar gum(GG), hupu gum(HG) and xanthan gum(XG)] were weighed at selected ratios of 1:1, 1:2, and 1:3; and transferred them to a small glass-mortar, the mixture was kneaded for 45 minutes by adding 1-2 ml of methanol. The resulting wet mass was dried in hot air oven at 45ºC for 24 hours. The dried dispersions were pulverized and passed through sieve No. 80. The prepared dispersions were stored in glass vials and used for further studies[10, 11]. The formulation codes are as follows: MD1-MA:GG-1:1; MD2- MA:GG-1:2; MD3- MA:GG-1:3; MD4- MA:HG-1:1; MD5- MA:HG-1:2; MD6- MA:HG-1:3; MD7- MA:XG-1:1; MD8- MA:XG-1:2 and MD9- MA:XG-1:3.

Evaluation of solid dispersion

Fourier Transform Infrared (FT-IR) study

Fourier Transform Infrared (FT-IR) spectrum of mefenamic acid and solid dispersions of guar gum, hupu gum and xanthan gum were recorded in a Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analysis of Mefenamic acid solid dispersions prepared using guar gum; hupu gum and xanthan gum were recorded with Netzsch DSC 200PC (Netzsche, Selb, German). The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5°/min was employed over a temperature range of 0- 350°with nitrogen purging. Powder sample was weighed into an aluminium pan was used as reference.

Drug content

Prepared mefenamic acid solid dispersions equivalent to 10 mg of mefenamic acid were accurately weighed and transferred to 100 ml standard flask and the volume was adjusted to 100 ml with phosphate buffer (pH 6.8), filtered through 0.45 μm nylon filter and absorbance was read at 285 nm.

Saturation solubility

Excess mefenamic acid and its different dispersions were introduced separately into the amber colored vials with 25 ml capacity, each containing 25 ml of distilled water and shaked for 24 hours at room temperature. The content of each vial was then filtered through 0.45 μm nylon filter. The filtrate was then diluted with distilled water and assayed spectrophotometrically.

pH -dependent solubility

The pH-dependent solubility of mefenamic acid and its solid dispersions were determined in pH 1.2, pH 6.8 and pH 7.4 buffers using the procedure of above saturation solubility.

Phase solubility

Phase solubility studies of mefenamic acid were carried out to evaluate the possible solubilising effect of the carrier by adding an excess of drug to 10 ml of pH 6.8 phosphate buffer containing increasing concentrations of guar gum, hupu gum and xanthan gum (0-1% w/v) and shaken at 25°C for 24 hrs. Drug concentration was determined spectrophotometrically at 285 nm. The apparent stability constant (K_c) of the drug-gums was calculated according to the following Higuchi-Connor's equation.[12]

$$K_C = \frac{slope}{S_0} \times (1 - slope)$$

In above equation, K_c indicated the apparent stability constant and slope was obtained from the linear portion of the phase solubility diagram and S_0 was the aqueous solubility of mefenamic acid.

Dissolution study
The dissolution test was carried out by using USP type-II (paddle method). The dissolution conditions includes, dissolution medium (phosphate buffer pH 6.8), temperature (37±0.5°C), speed of rotation (50 rpm) and volume (900 mL). Mefenamic acid containing prepared solid dispersions equivalent to 10 mg were placed in the basket of dissolution medium and the apparatus was run. The 10 ml aliquot was withdrawn at specific intervals of up to 60 min and replaced same with fresh dissolution medium. The samples were filtered through 0.45 µm nylon filter, absorbances were recorded and concentrations were calculated using standard graphic.

Release kinetics
To investigate the possible mechanisms of mefenamic acid release from the prepared solid dispersion, the drug release data were fitted to Higuchi, Zero-order, First-order, Hixson Crowell, Erosion, Baker- Lonsdale, Weibull and Korsmeyer's peppas kinetic models.

Fabrication of pulsincap
Pure mefenamic acid (MA) PC1, solid dispersions of mefenamic acid - guar gum (1:3) ratio (MA-GG) PC2, mefenamic acid - hupu gum (1:3) ratio (MA-HG) PC3, mefenamic acid - xanthan gum (1:3) ratio (MA-XG) PC4 were selected in filling the pulsincaps.

Preparation of insoluble capsule bodies
Cross-linked capsule
Cross-linking of gelatin molecules was achieved by exposing to formalin vapours. Cross-linking involves the reaction of amino groups in gelatin molecular chain with aldehyde groups of formaldehyde by a schiff's base condensation so that gelatin becomes water insoluble[13].

Method of cross-linking the capsule bodies
The cap and bodies of hard gelatin capsules were separated. Formaldehyde (15%) was taken into a desiccator and a pinch of potassium permanganate was added to it until formalin vapours were produced. The bodies were placed on a wire mesh in the dessicator and exposed to formalin vapours. The reaction was carried out for 6/12/24 hrs after which bodies were removed and dried at 50°C for 48 hrs in hot air oven[14] to complete the reaction between gelatin and formalin vapour[15]. The bodies were then dried at room temperature to assist removal of residual formaldehyde[16].

Preparation of hydrogel plug
Plug was prepared as compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap. A tight fit between the plug and the impermeable capsule shell is essential to regulate water penetration to the capsule content and drug release prior to complete erosion of plug material. Ideally, the plug should erode only from the surface exposed to the release medium. Plug ejection can be done by swelling

when contact with aqueous fluids or pushing out by increased internal pressure or erosion or by enzyme degradation[17].

Capsule filling

Solid dispersions of mefenamic acid and pure mefenamic acid were filled in the capsule bodies and plugged with hydrogel plug.

Sealing and coating of capsules

The treated body and the cap of the capsules were sealed with a small amount of 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with enteric coating to reduce variability in gastric emptying time.

Evaluation of pulsincap
In-vitro dissolution study

Dissolution studies were carried out using USP dissolution type-I (basket method) apparatus. Capsules were placed in the basket and immersed completely in dissolution media. In order to simulate the pH changes along the GI tract, three dissolution media of buffer pH 1.2, 7.4 and 6.8 were sequentially used. When performing experiments, the pH 1.2 medium was first used for 2 hr (since the average gastric emptying period is 2 hr), then removed and add fresh buffer of pH 7.4, dissolution was carried out for 3 hrs, after that replace the medium with fresh pH 6.8 phosphate buffer. A total of 900 ml of the dissolution medium was used at each time. Rotation speed was 50 rpm and temperature was maintained at 37ºC. A 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analysed by UV spectroscopy and the cumulative percentage release was calculated over the sampling times.

Release kinetics

To investigate the possible mechanisms of mefenamic acid release from the prepared pulsincap, the drug release data were fitted to various models such as Higuchi, Zero-order, First-order, Hixson Crowell, Erosion model, Baker- Lonsdale, Weibull and Korsmeyer's peppas kinetics.

RESULTS AND DISCUSSION

Solid dispersions

FTIR:

Comparative FTIR spectra are depicted in the Figure 1. From the FTIR results, it was observed that there exists no physical interaction as there were no changes in the peaks of finger print region obtained in the mefenamic acid spectrum to that of the spectra of mefenamic acid solid dispersions of guar gum, hupu gum and xanthan gum.
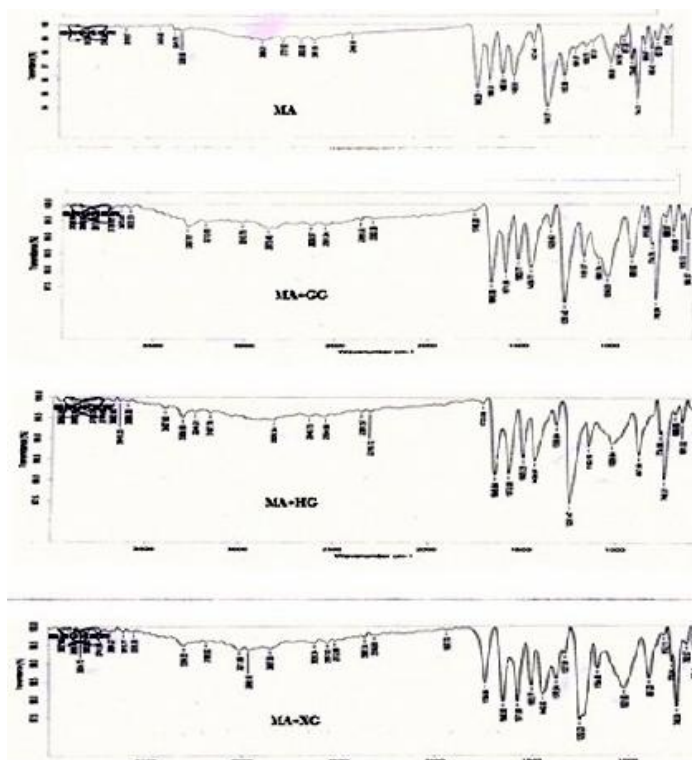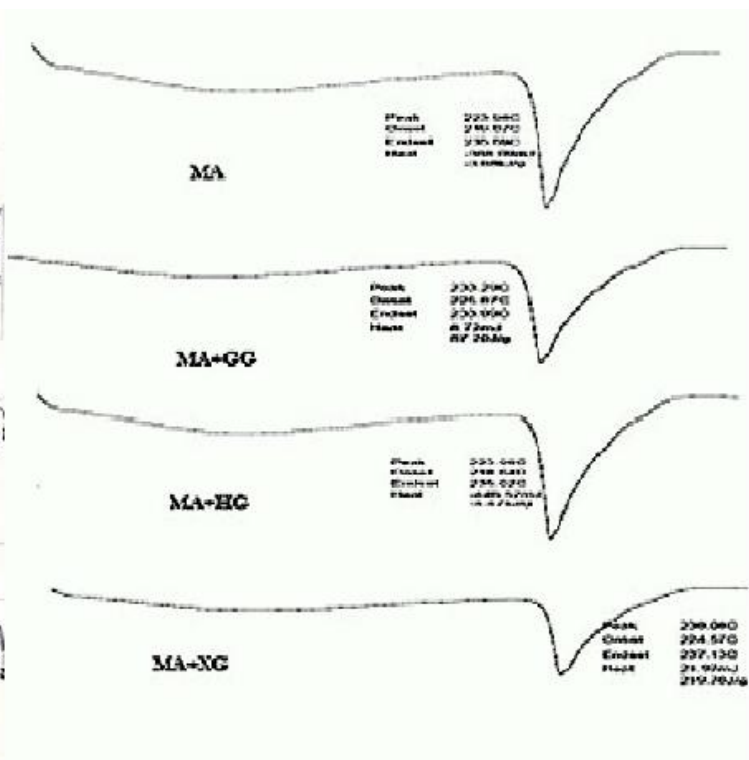
Figure No.1: Comparative FTIR spectra

Figure No.2: DSC analysis of Solid dispersions

DSC

The DSC thermograms are shown in the Figure 2. The DSC thermogram of mefenamic acid exhibited endothermic peak at 223.98°C, mefenamic acid solid dispersion of guar gum at 233.29°C, mefenamic acid solid dispersion of hupu gum at 223.98°C and mefenamic acid solid dispersion of xanthan gum at 238.08°C. The results depicted that there exists a slight variation in the endothermic peaks of mefenamic acid to that of mefenamic acid solid dispersions.

%Practical Yield and Drug Content:

Percentage practical yield of mefenamic acid solid dispersions was in the range of 91.71-95.65. The percentage yield was low for MD3 and the high for MD7. Drug content was in the range of 75.86-83.03. This indicated that mefenamic acid was uniformly distributed in all the solid dispersions. The drug content was low for MD1 and high for MD6. Percentage practical yield and drug content of mefenamic acid solid dispersions are tabulated in the Table 1.

Solubility studies:

The solubility of the prepared solid dispersions was found to be high when compared to pure drug. This may be due to the improvement of wetting of drug particles and localized solubilization by the hydrophilic polymers[18]. The solubility of MD3 was high. pH dependent solubility studies of mefenamic acid and its solid dispersions was carried out in solutions of different pH such as 1.2, 6.8 and 7.4. It was observed that solubility was high in pH 6.8 and low in 1.2. The results indicated that the solubility of mefenamic acid was high in basic conditions and low in acidic conditions. The solubility studies of mefenamic acid solid dispersions are shown in Figure 3.

Table 1: Percentage Practical Yield and Drug Content

S. No.	Formulation Code	%Practical Yield	% Drug Content ± S.D. (n=6)
1	MD1	94.88	75.86±0.99
2	MD2	92.39	76.65±1.37
3	MD3	91.71	78.23±1.69
4	MD4	92.68	78.51±0.92
5	MD5	93.82	82.03±1.04
6	MD6	92.98	83.03±0.97
7	MD7	95.65	78.13±1.58
8	MD8	91.98	80.51±0.59
9	MD9	92.57	79.96±1.54
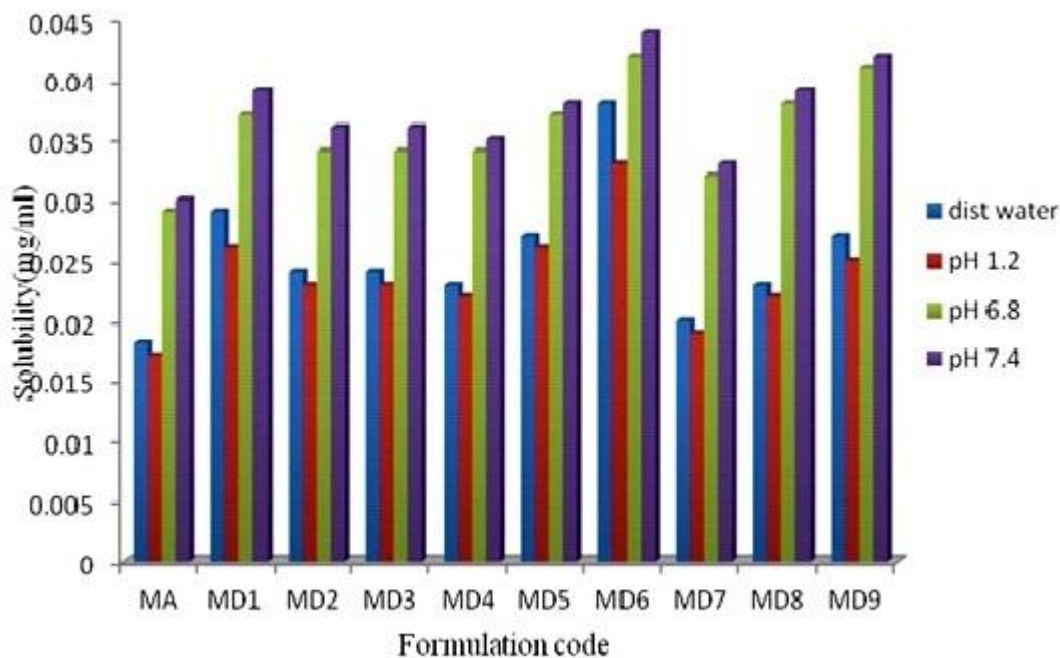
Figure No. 3: Solubility studies of Mefenamic acid

Phase Solubility studies:

Phase solubility studies were carried out for mefenamic acid in different concentrations of guar gum, hupu gum and xanthan gum and it was found to be more in hupu gum (Figure 4) and K_c values obtained were found to be $0.6043 M^{-1}$, $0.3313 M^{-1}$, $0.55 M^{-1}$ respectively.
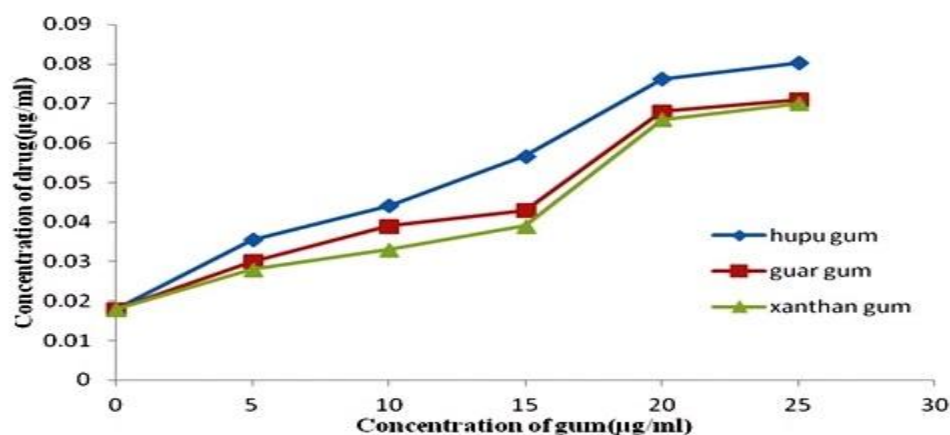
Figure No. 4: Phase Solubility studies of Mefenamic acid

Dissolution profile of mefenamic acid solid dispersions

Dissolution studies for MA and its solid dispersions were carried out using phosphate buffer pH 6.8 as dissolution medium (Figure 5). All the solid dispersions showed improved dissolution of MA over that of pure MA. Guar gum dissolves and thereby forms pores filled with aqueous fluid through which the drug can diffuse. In case of xanthan gum, the release of drug occurs by swelling as well as erosion. The order of drug release from the solid dispersions prepared by different gums are as follows HG>GG>XG. The order of drug release from the solid dispersions prepared by different ratio are as follows 1:3>1:2>1:1. In kneading technique, synergistic effect of trituration and solubilization effect of solvent used usually leads to an improvement in dissolution rate. The improved dissolution of MA may also be attributed to increased wettability and thereby the solubility due to the higher level of hydrophilicity by the usage of polymers[18] (Table 2).

Table 2: Dissolution parameters of mefenamic acid solid dispersions

S. No.	Formulation Code	DE_{30}	DE_{60}	T_{50}
1	MA	21.36	22.09	0.00
2	MD1	41.07	43.3	31.94
3	MD2	47	47.77	23.58
4	MD3	49.94	50.7	20.33
5	MD4	48.81	49.12	20.21
6	MD5	50.12	50.81	17.68
7	MD6	57.86	56.78	10.99
8	MD7	40.71	42.26	32.76
9	MD8	43.66	45.45	27.61
10	MD9	47.06	48.39	23.60

Release Kinetics of Mefenamic acid solid dispersions:

The drug release profiles from the mefenamic acid and its solid dispersions were fitted to various kinetic models such as zero order, first order, Higuchi, Peppas, Hixson-Crowell, Erosion, Baker-Lonsdale and Weibull models. The kinetics study was used to elucidate the mechanisms of drug transport by comparing the release data to mathematical models. The values of correlation coefficient (r) and release rate constants (K) from different models calculated for mefenamic acid solid dispersions are given in Table 3.

Table 3: Release Kinetics of Mefenamic acid solid dispersions

Formulation code		Zero order model	First order model	Higuchi model	Peppas release model	HixsonCrowell model	Erosion model	Baker Lonsdale model	Weibull model
MA	r	0.9622	0.9701	0.9995	0.9994	0.9674	0.9674	0.9998	0.9986
	k	1.2113	0.0135	4.9487	0.6438	0.0202	0.0043	0.0005	0.2393
MD_1	r	0.9387	0.9813	0.9897	0.9696	0.9718	0.9718	0.9896	0.9837
	k	2.1244	0.0265	9.4517	0.4125	0.038	0.0082	0.0021	0.607
MD_2	r	0.912	0.975	0.9848	0.993	0.9597	0.9597	0.9938	0.9926
	k	2.6231	0.0349	11.5011	0.3581	0.0489	0.0105	0.0025	0.6934
MD_3	r	0.9074	0.9767	0.981	0.986	0.9608	0.9608	0.992	0.989
	k	2.744	0.0372	12.1867	0.3335	0.0518	0.0112	0.0029	0.7807
MD_4	r	0.9193	0.9797	0.9924	0.9996	0.9634	0.9634	0.9995	0.9995
	k	2.787	0.0377	11.8263	0.3892	0.0526	0.0113	0.0028	0.7469
MD_5	r	0.9015	0.9713	0.9785	0.9998	0.9561	0.9562	0.9864	0.9945
	k	2.9281	0.0407	12.7945	0.3282	0.0562	0.0121	0.0033	0.7764
MD_6	r	0.8868	0.9777	0.9801	0.9992	0.9549	0.9549	0.9969	0.9957
	k	3.3536	0.0498	14.5706	0.2985	0.0671	0.0145	0.0045	0.9763
MD_7	r	0.9381	0.9793	0.9974	0.9984	0.9682	0.9682	0.9985	0.9999
	k	2.4213	0.0311	10.1188	0.4467	0.0441	0.0095	0.002	0.5806
MD_8	r	0.937	0.9846	0.9934	0.9872	0.9735	0.9736	0.995	0.9905
	k	2.3341	0.0298	10.1586	0.4136	0.0424	0.0091	0.0023	0.663
MD_9	r	0.9263	0.9831	0.9906	0.9922	0.9701	0.9701	0.995	0.9917
	k	2.582	0.0341	11.2389	0.3815	0.0479	0.0103	0.0027	0.734

The correlation coefficient of MD4, MD5, MD6 and MD9 is high for Peppas model suggesting that they follow Peppas release kinetics. This means the release mechanism is swelling and relaxation of polymer. The correlation coefficient of MD2, MD3, MD8 is high for Baker-Lonsdale model suggesting that they follow Baker-Lonsdale release kinetics which describes the controlled release of a drug from a spherical matrix. The correlation coefficient of MD1 is high for Higuchi model suggesting that it follows Higuchi release kinetics which states that drug release is a diffusion process. The correlation coefficient of MD7 is high for Weibull model suggesting that they follow Weibull release kinetics. However the 'r' value ranging between 0.8868–0.9999 suggests that more than one type of release phenomenon could be involved.

Dissolution studies of mefenamic acid pulsincap:

The dissolution profiles of MA pulsincaps were reported in the Figure 6. % drug release of MA pulsincaps prepared with pure MA, MA-GG solid dispersions, MA-HG solid dispersions and MA-XG solid dispersions was found to be 41.25, 91.44, 93.87and 88.4 respectively. Dissolution parameters of Mefenamic acid pulsincaps are given in the Table 4. During the dissolution studies of pulsincaps, the outer coat which was made by ethylcellulose for all formulations remained intact for 2 hours in pH 1.2 and dissolved in intestinal pH, leaving the soluble cap of the capsule. The exposed polymer plug then absorbed the surrounding fluid and swelled. After entire wetting of the plug, it formed a soft mass, which was easily ejected out of the capsule body, releasing the drug formulation into dissolution medium[19]. Upon contact with the colonic fluid, the natural polysacharides slowly begins to hydrate from the edge towards the centre forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the gums into the colonic medium[20, 21]. The dissolution profiles of MA pulsincaps prepared with MA-GG solid dispersions, MA-HG solid dispersions and MA-XG solid dispersions were very high than that of pure MA containing pulsincap. The pulsincap filled with MA-HG solid dispersions showed highest drug release at the end of 12 hr. The release of drug from the modified pulsincap was proportional to the concentration of the polymer.

Table 4: Dissolution parameters of Mefenamic acid Pulsincap

S. No.	Formulation Code	DE_{30}	DE_{60}	T_{50}
1	PC1	2.87	4.79	0.00
2	PC2	5.41	10.63	6.70
3	PC3	6.15	12.56	6.41
4	PC4	4.9	9.46	7.10

Release Kinetics of Mefenamic acid Pulsincap:

The drug release profiles from the MA pulsincaps were fitted to various kinetic models such as zero order, first order, Higuchi, Peppas, Hixson-Crowell, Erosion, Baker- Lonsdale and weibull models. The values of correlation coefficient (r) and release rate constants (K) from different models calculated for MA pulsincaps are given in Table 5.

The correlation coefficient of PC1 is high for Peppas model indicating that it follows peppas release kinetics. The correlation coefficient of PC2 and PC4 is high for Baker-Lonsdale model suggesting that they follow Baker-Lonsdale release kinetics. The correlation coefficient of PC3 is high for Higuchi model suggesting that it follows Higuchi release kinetics. However the 'r' value ranging between 0.9209–0.9999 suggests that more than one type of release phenomenon could be involved.

Table 5: Release Kinetics of Mefenamic acid Pulsincap

| Formulation code		Zero order model	First order model	Higuchi model	Peppas release model	Hixson-Crowell model	Erosion model	Baker - Lonsdale model	Weibull model
PC1	r	0.9994	0.9993	0.9733	0.9999	0.9992	0.9997	0.9345	0.9564
	k	3.5696	0.0449	11.8334	1.4259	0.0642	0.0138	0.0028	0.3865
PC2	r	0.9822	0.9801	0.9933	0.9706	0.9809	0.9807	0.9998	0.9462
	k	8.8725	0.2019	29.5845	1.6469	0.2268	0.0489	0.0237	1.7061
PC3	r	0.9706	0.9651	0.9949	0.9731	0.9659	0.9655	0.982	0.9209
	k	9.5503	0.2318	31.2978	1.627	0.2499	0.0538	0.0274	1.9698
PC4	r	0.9818	0.9789	0.9966	0.9738	0.9799	0.98	0.9999	0.9414
	k	8.3454	0.1781	28.045	1.6538	0.2072	0.0446	0.0207	1.5018
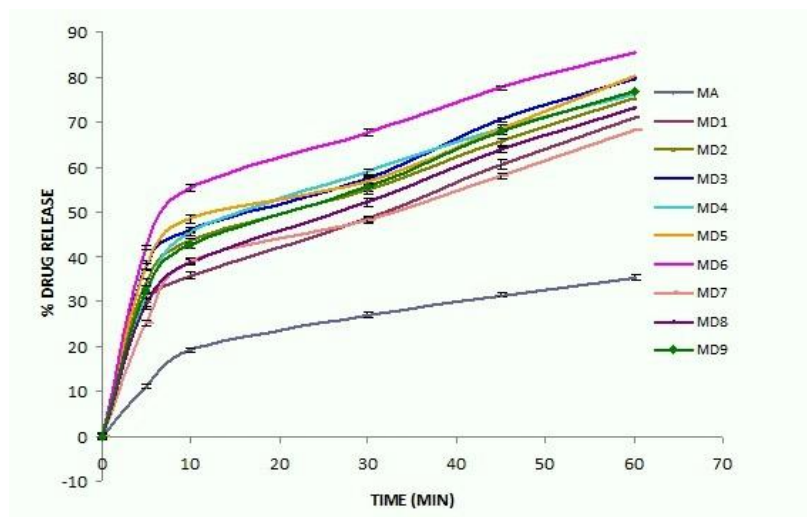
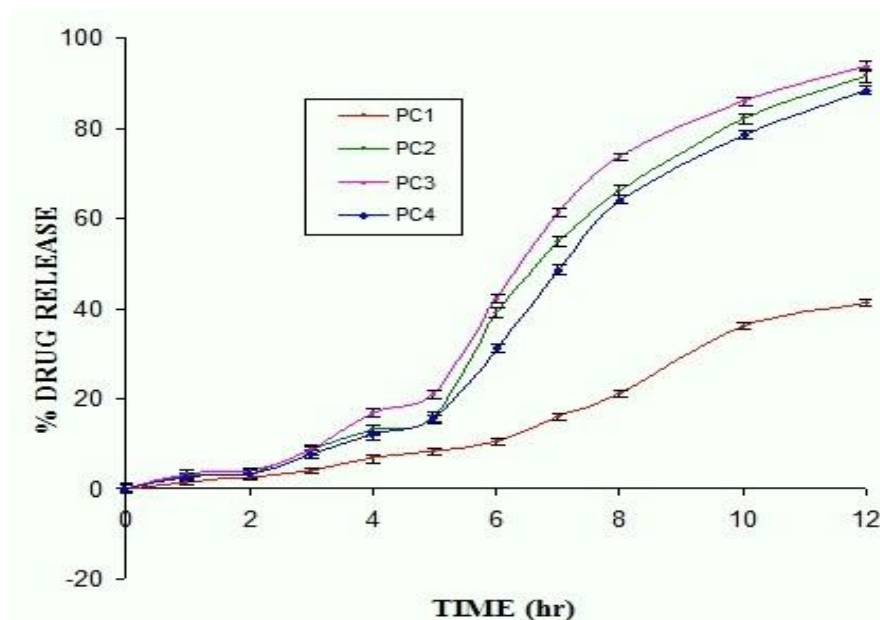Figure No.5: Dissolution profile of Mefenamic acid and its solid dispersions

Figure No.6: Dissolution profile of Mefenamic acid pulsincaps

CONCLUSION

As Mefenamic acid is poorly water soluble drug, its solubility was enhanced by solid dispersion technique using natural polysaccharides like guar gum, hupu gum and xanthan gum as carriers. Modified pulsincap delivery of Mefenamic acid was formulated by filling the insoluble hard gelatin capsules with Mefenamic acid and its solid dispersions and sealing with a hydrogel plug (Hupu gum). The results of the evaluation studies indicated that there was a significant drug release only in the colonic region. Although the availability of colonic fluid is less, gums absorb even that little amount of colonic fluid, swell and release the drug in the colon. On the basis of the results it was concluded that mefenamic acid can be delivered successfully to the colon by modified pulsincap technique.

ACKNOWLEDGMENT

REFERENCES:

1. Macfarlane GT, Cummings JH, Macfarlane S and Gibson GR. Influence of retention time on degradation of pancreatic enzymes by colonic bacteria grown in 3-stage continuous culture system. J. Appl. Bacteriol. 1989; 6: 521-527.
2. Abdul B and John B. Perspectives on Colonic Drug Delivery. Business BriefingL: Pharmatech. 2003; 185–190.
3. Smolensky MH and Peppas NA. Chronobiology, drug delivery and chronopharmaceutics. Adv. Drug. Deliv. Rev. 2007; 59: 828–851.
4. Maroni A, Zema L, Cerea M and Sangalli ME. Oral pulsatile drug delivery systems. Expert Opin. Drug. Deliv. 2005; 2: 855–871.

5. Gazzaniga A, Palugan L, Foppoli A and Sangalli ME. Oral pulsatile delivery systems based on swellable hydrophilic polymers. Eur. J. Pharm. Biopharm. 2008; 68: 8–11.

6. Wilding IR, Davis SS, Bakhshaee M, Stevens HNE, Sparrow RA and Brennan J. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Pharm. Res. 1992; 9: 654-657.

7. Hebden JM, Wilson CG, Spiller RC, Gilchrist PJ, Blackshaw E, Frier ME and Perkins AC. Regional differences in quinine absorption from the undisturbed human colon assessed using a timed release delivery system. Pharm. Res. 1999; 16(7): 1087-1092.

8. Burns JS, Stevens HNE, McEwen J, Pritchard G, Brewer FM, Clarke A, Johnsons ES and McMillan I. Pulsatile drug delivery system. J. Cont. Rel. 1996; 38: 151-158.

9. Arun Rasheed and Ashok Kumar CK. Synthesis, hydrolysis and pharmacodynamic profiles of novel prodrugs of mefenamic acid. Int. J. Cur. Pharm. Res. 2009; 1: 47-55.

10. Lalit J and Tapar KK. Preparation and characterization of mefenamic acid solid dispersions by kneading method. Int. J. Pharm. Sci. Res. 2011; 2: 2623-2628.

11. Yadav AV and Yadav VB. Improvement of physicochemical properties of mefenamic acid with hydrophilic carriers by solid dispersion (kneading) method. Res. J. Pharm. Tech. 2008; 1: 422-425.

12. Higuchi T and Connors KA. Phase-solubility techniques. Adv. Anal. Chem. Instrum. 1965; 4: 117–212.

13. Franenkel-Conrat H and Olcott HS. Reaction of formaldehyde with proteins II participation of guanidyl groups and evidence of crosslinking. J. Amer. Chem. Soc. 1946; 68:34.

14. Bajpai SK, Bajpai M and Dengre R. Chemically treated hard gelatin capsules for colon targeted drug delivery: A novel approach. J. Appl. Poly. Sci. 2003; 89: 2277-2282.

15. Abraham S and Srinath MS. Development of modified pulsincap drug delivery system for drug targeting. Ind. J. Pharm. Sci. 2007; 59: 24-27.

16. Avinash RT and Surendra GG. Development and evaluation of pulsatile drug delivery system using novel polymer. Pharm. Dev. Tech. (2009) 14: 380-387.

17. Kikuchi A and Okano T. Pulsatile drug release control using hydrogels. Adv. Drug. Del. Rev. 2002; 54: 53-77.

18. Saquib Hasnain M and Amit Kumar Nayak. Solubility and dissolution enhancement of ibuprofen by solid dispersion technique using peg 6000-PVP K30 combination carrier. Bulg. J. Sci. Ed. 2012; 21: 118-132.

19. Gayatri Patel C and Madhabhai Patel M. Developing a modified pulsincap system. Pharmaceutical Technology Europe 2009; 21.

20. Colombo P, Conte U, Caramella C, Gazzaniga A and Manna L. Compressed polymeric mini-matrices for drug release control. J.Contr. Rel. 1985; 1: 283–289.

21. Colombo P, Bettini R, Massimo G, Santi P and Peppas NA. Drug diffusion front movement is important in drug release control from swellable matrix tablets. J. Pharm. Sci. 1995; 84: 991–997.

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