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In vitro Release kinetics and Bio availability of Layered Matrix tablets of Diclofenac Sodium

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Abstract

Controlled release tablets having near zero-order release of diclofenac sodium water soluble drug were prepared using guar gum (GG) in matrix core and Hydroxy Propyl Cellulose (HPC), Hydroxy Propyl Methyl Cellulose (HPMCK4M) and Sodium Carboxy Methyl Cellulose (Na CMC) as barrier layers. The optimum ratio of drug: guar gum was found to be 1:1, anionic GG in the matrix core and anionic Na CMC as barrier layers resulted in near zero order release of diclofenac sodium. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. The nature of drug release from matrix tablets and layered matrix tablets followed non-Fickian diffusion and super case II mechanism respectively. Mean dissolution time (MDT) for the formulations MT-GG and MLT-06 were found to be 3.65h and 16.57h, while Dissolution Efficiency (DE_8%) decreases, indicating that the release of drug is slower from layered matrix tablets. On the basis of in vitro release data, MLT-06 was subjected to bioavailability studies. The in-vivo characterization of diclofenac sodium in human volunteers from formulation MLT-06 showed delayed T_{max} unaltered bio availability indicating a slow and controlled release of the drug from layered matrix tablets.

Key words: Diclofenac sodium, Matrix and layered matrix tablets, Controlled released.

Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet [1]. One to three multi layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during tabletting process [2]. The modulating layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate [3]. In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and surface available for drug release slowly increases. In this way the decrease of delivery rate due to increase in diffusion path length (saturation effect) is counter balanced by the simultaneous increase of the area available for drug release [4, 5]. Thus by combining a time-dependent control of the hydration rate of the

device with the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile. Diclofenac sodium is a potent non steroidal anti inflammatory drug (NSAIDs) of aryl acetic acid class used for the treatment of degenerative joint disease such as osteoarthritis, anklylosing spondylitis, rheumatoid arthritis and also has both analgesic and antipyretic properties [6]. Diclofenac sodium has a pKa value of 4. Diclofenac sodium is practically insoluble in acidic solution, but dissolves in intestinal fluids. To diminish diclofenac sodium gastrointestinal (GI) irritation, effective enteric coating or sustained release dosage forms have been developed. Thus the present study was carried out to investigate the usefulness of layered matrix tablets in providing oral controlled drug delivery of diclofenac sodium.

Experimental

Materials

Diclofenac sodium was gift sample from M/s (Amoli Organic Ltd., Mumbai, India. Naproxen gift sample from M/s (Granules India Ltd., Hyderabad, India) Guar gum, from H.B gums Kalol, Gujarat, India., Sodium Carboxy Methyl Cellulose (Na CMC) (high viscosity grade), was gift samples from Reliance Cellulose Product, Hyderabad. India, Hydroxy Propyl Cellulose (HPC) and Hydroxy Propyl Methyl Cellulose (HPMC K4M) were gift samples from colorcon Asia Pvt Ltd Goa, India. Lactose, talc, magnesium stearate were procured from M/s Loba Chime Pvt. Ltd. Mumbai. All other chemicals and reagents used were of analytical grade

Method

Preparation of matrix and layered matrix tablets of diclofenac sodium

Matrix core granules were prepared by wet granulation process using hydrophilic polymer Guar gum, lactose was used as diluent, starch paste 10% was used as binding agent. The wet mass was screened through sieve no14 and the granules were dried at 50^{o}C for 1hr in a tray dryer. The dried granules were passed through sieve No18 and lubricated with a mixture of talc and magnesium stearate. The barrier layers containing HPC, HPMC K4M and Na CMC were prepared by wet granulation method. The polymers and 10% starch paste were mixed well the resulting wet mass was passed through sieve no 14 and air dried at 30^{o}C for an hour, mixed with talc and magnesium stearate.

Compression of layered matrix tablets

Formulation of layered matrix tablets was made using guar gum and drug loaded matrix core granules and barrier layer granules. Initially the volume of die cavity was adjusted equivalent to total weight of layered matrix tablet (400mg, 450mg). Then pre weighed amount of barrier granules i.e. HPC, HPMCK4M and Na CMC granules equivalent to bottom layer (50mg & 75mg) were taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and 300mg of matrix core granules were placed over the bottom layer of polymer granules in the die cavity and again slightly compressed. The remaining volume of die cavity was filled with pre weighed amount of barrier granules equivalent to top layer (50mg & 75mg) and finally compressed on a Rotary compression machine (Riddhi, Ahmedabad, India). The hardness of tablet was maintained in the range of 4-5kg/cm^2

In Vitro Drug Release Study

Drug release was studied using a dissolution apparatus type 2 (Lab India, DISSO 2000, Mumbai, India) with a shaft at a speed of 50 rpm. To study the effect of dissolution medium, drug release was studied in 900-mL HCl of pH 1.2 for 2 hours and then the pH of medium was raised to 6.8 by adding 4.6g Sodium hydroxide, 3.06g mono basic potassium phosphate and 4.005g dibasic sodium phosphate at 37±1°C for 12h. Samples were collected at specific time intervals and assayed by a UV spectrophotometer (Elico, Model SL-150, Mumbai, India.) at a wavelength

of 276 nm. During the drug release studies, the tablets were observed for physical integrity. The experiments were repeated three times and results were taken as average of three test readings with standard deviations. The accuracy and precision of the standard curve was sufficiently accurate, with a validated linearity for determination of drug in dissolution media.

Analysis of release data

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$

Where M_t is the amount of drug dissolved at time t, M_o the initial amount of drug, $K_1$is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and n is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient (r^2) was used as an indicator of the best fitting, for each of the models considered.

The following equation was used to calculate the other dissolution parameters D.E_8% and MDT mean dissolution data [7]

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad \text{------ Eq.[1]}$$

Mean dissolution time (MDT) is a measure of the rate of the dissolution process calculated from the amount of drug released to the total cumulative drug. To compare the results of dissolution tests of different formulations: Dissolution efficiency (D.E) [8] after 8hr of release test was used.

$$DE_8\% = \frac{\int_0^t y\, dt}{y_{100}\, t} \times 100 \text{ ----- Eq.[2]}$$

The similarities between two dissolution profiles were assessed by a pair wise model independent procedure similarity factor (f_2).

Similarity factor

$$f_2 = 50 Log\left\{\left[1 + \frac{1}{n\sum_{n=1}^{n=i}(R_t - T_t)^2}\right]^{-0.5} \times 100\right\} \quad \text{--- Eq.(3)}$$

Where n is the sampling number, R_t and T_t are the percent dissolved of the reference and test products at each time point t. Where W_t is the optional weight factor (normally taken as 1). f_2 values should be close to 100. In general f_2 values higher than 50 (50-100), show the similarity of dissolution profiles [7].

In vivo Bio availability Study

Eight male volunteers, aged between 23 and 25 years and weighing between 62 and 68kg participated. Studies were conducted with permission from the institutional ethical committee. The protocol of study of was approved by the Human Ethical Committee, University College of Pharmaceutical Sciences, Kakatiya University, India, with reference number UCPSc/BA/2009-06.which compiled ethical to the Helsinki Declaration. The purpose of the study was fully explained to the volunteers and an informed written consent was obtained from each volunteer. This study was performed in a two-way crossover design with a washout period of one week between two phases. No other drugs were taken during the study period. The subjects were randomly divided into two groups. A light breakfast was served to all volunteers on the study day after overnight fasting, followed by administration of MLT-06 to one group and Voveran SR tablet to another group with a glass of water after half an hour of breakfast. No food was allowed until 4 hrs after dosing. Approximately 5 ml of blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24hrs. Samples were centrifuged at 3000 rpm for 10 minutes and Serum was stored at -20°c until analyzed by the modified method of El-sayed et al. [9]

Table 1: Formulae of matrix and layered matrix tablets with guar gum as matrix core.

Ingredients (mg)/Formulation	Diclofenac Sodium	Guar Gum	Lactose	HPC	HPMC K4M	NaCMC	Starch	Talc	Mg stearate
MT -GG	100	100	70	-	-	-	18	8	4
MLT-01	100	100	70	100	-	-	18	8	4
MLT-02	100	100	70	150	-	-	18	8	4
MLT-03	100	100	70	-	100	-	18	8	4
MLT-04	100	100	70	-	150	-	18	8	4
MLT-05	100	100	70	-	-	100	18	8	4
MLT-06	100	100	70	-	-	150	18	8	4

High-Performance Liquid Chromatography Determination of Diclofenac sodium in Human serum

To each of 0.5 ml of human serum 100µl of naproxen (1µg) as internal standard were added mixed thoroughly. Then 500µl of 500mM HCl was added and mixed for 3 minutes. This was then extracted with 5ml of dichloromethane in vortex mixer for 5minutes and phase separation was achieved by centrifugation for 10 mins. From each sample, 4ml of organic layer was transferred to a test tube for removal of solvent by evaporation using temperature regulated vacuum oven. Each sample residue was reconstituted in 0.1 ml of acetonitrile, then vortexed for one minute and 20µL injected into HPLC equipment. The operating HPLC conditions were set, and a stable base line was obtained on the recorder at a flow rate of 1ml/min. Then 20µL of the reconstituted solution was spiked; Peak area of the drug and internal standard were measured and their ratios were computed. The retention time of diclofenac and naproxen were 6.48min and 4.50min respectively.

Pharmacokinetics data analysis

The data obtained from diclofenac serum concentration time profile, were analyzed for each subjects using non compartmental method. The Pharmacokinetics parameters were estimated by using KINETICA^{TM} Soft ware (INNA Phase Corp., 2000)

Statistical Analysis

The data obtained was statistically analyzed using a using Graph pad prism version 4. (Graph pad prism Software, Inc). Paired t-test was used for comparison of all the Pharmacokinetic parameters. A value of $P<0.05$ was considered to be significant and results were expressed as mean± SD.

Results and Discussion

Physico chemical characterization of matrix and layered matrix tablets

The physical parameters such as hardness was ranked from 4.04±0.11 kg/cm^2 to 4.99±0.12kg/cm^2, thickness ranked from 4.04±0.03mm to 6.07±0.06mm, friability ranked from 0.251±0.02% to 0.840±0.01%, mass of the tablets ranged from 301.5±0.16 to 451.0 ±1.16(mg) and drug content in the range of 98.50± 0.78% to 103.2± 2.65% of the formulations. The hardness and thickness of the tablets were increased as the amount of barrier layers was increased. The hardness of layered matrix tablets tended to increase and friability decreased.

In vitro drug release and kinetic characteristics

Apparent drug release prolongation could be attained for the layered matrix tablets. The percentage drug release from formulations MT-GG and MLT-01 to MLT-06 ranged from 98.13±1.130% and 96.3±1.12% to 50.5±1.14%,

Thus on the basis of drug release data, it is evident that as thickness of the polymer layer increased the rate of drug release was found to be decreased. Na CMC layered tablets (MLT-05 and MLT-06) provided the desired release rate compared to HPC and HPMC K4M layered tablets (MLT-02 and MLT-04), hence linearization has been achieved. The higher co-relation coefficient (r^2) indicated a superiority of the dissolution profile to the mathematical equations. The matrix tablets (MT GG) shows higher (r^2) values for the first order kinetics (r^2 =0.914) Table 2, indicated that diclofenac sodium released from matrix tablets followed first order kinetics. It was observed that the edges of layers were rounded off due to slight erosion of swollen barrier layers of HPC and HPMCK4M. The strength of viscous gel layer around the matrix core generally depends on the viscosity of the polymer used. The results indicated that anionic and pH dependent polymer Na CMC does not fully hydrate when placed in 0.1 N HCl, but when the dissolution media was replaced with pH 6.8 it showed rapid hydration and forms a viscous gel layer that forming a loose porous on the surface of the tablet facilitating the matrix core seeping of diclofenac sodium from the surfaces of the matrix core resulting in constant delivery of the drug [10].

Table 2. Release kinetics, MDT and DE_8% of guar gum matrix and layered matrix tablets of diclofenac sodium.

Formulation code	Zero order release rate mgh^{-1}	(r^2)	First order rate constant (h^{-1})	(r^2)	Release exponent (n)	(k)	DE_8 %	MDT (h)	f_2
Voveran SR	7.29	0.803	0.42	0.979	0.48	1.55	96.84	2.68	---
MLT-G	7.68	0.914	0.32	0.992	0.47	1.14	89.39	3.65	86.74
MLT-01	8.11	0.973	0.36	0.985	0.59	1.38	92.52	3.83	28.18
MLT-02	7.63	0.985	0.26	0.922	0.57	1.33	76.97	6.40	32.86
MLT-03	6.64	0.980	0.11	0.992	0.58	1.26	81.30	6.51	36.62
MLT-04	6.53	0.992	0.13	0.991	0.65	1.13	80.89	7.50	38.74
MLT-05	6.12	0.996	0.10	0.996	0.81	0.95	88.30	9.19	40.37
MLT-06	5.64	0.992	0.08	0.978	0.98	0.68	88.64	16.57	41.93

The release rate patterns of all the formulations are given in table 2. The results suggested that the developed layered matrix tablets showed zero-order or case II release. The values of kinetic constant (k) were in accordance with the values of n, the diffusional exponents, with k having lower values when the mechanism was Case II and higher values for the formulations that released the drug by non-Fickian diffusion. The diffusional exponents (n) values for all formulations ranged from 0.47 to 0.98. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. It was observed that layered tablets swelled indicating that absorption of dissolution media and swelling process were taking place simultaneously. This indicates that polymer relaxation had a role in drug release mechanism; as a result the release of drug was extended for over a period of more than 12hrs

Table 3. Pharmacokinetic Parameters (mean ±sd) following oral administration of MLT-06 and Voveran SR

Pharmacokinetic Parameters	Voveran SR	MLT-06
[a] **C_{max} (ng ml^{-1})**	553.75±21.88	275.48±5.40
[a] **T_{max}(hrs)**	3.43±0.67	6.00±0.00
Relative bioavailability (%)	----------	95.06
$AUC_{0-\infty}$ (ng hrs ml^{-1})	3789.84±29.62	4997.09±341.16
[a] **MRT (hrs)**	8.16±1.48	12.72±1.28

[a] Statistical significant (P< .05)

The independent statistical evaluation, which involves ratio tests are dissolution efficiency (DE_8%) and Mean dissolution time (MDT) and paired test is similarity factor (f_2). The data is shown in Table 2. MDT and DE_8% values of MT-GG and MLT-06 formulations were found to be 3.65h, 16.57h and 89.39%, 88.64% respectively. MDT is increased, while DE_8% decreased, indicating the release of diclofenac sodium is slower, which is attributed to increase in the thickness of barrier layers (Na CMC) on the matrix core. The results of f_2 values showed similar dissolution profiles for matrix tablets and layered tablets MT-GG (f_2=86.74) and MLT-06 (f_2=41.93). Hence layered tablets showed dissimilar dissolution profiles as shown in Table 2**,** with that of commercial (Voveran SR) sustained release tablets. The layered matrix tablets (MLT-06) was selected as a suitable formulation for the bioavailability study in

human volunteer, since results of in-vitro release of MLT-06 formulation showed slower drug release is shown in figure 1.

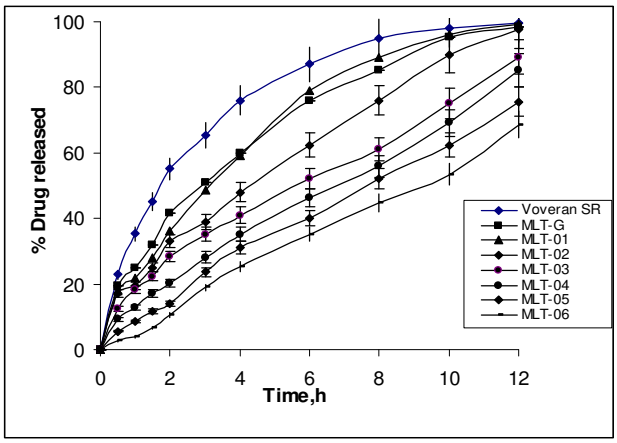

Figure1. In-vitro dissolution profiles of matrix and layered matrix tablets of diclofenac sodium.

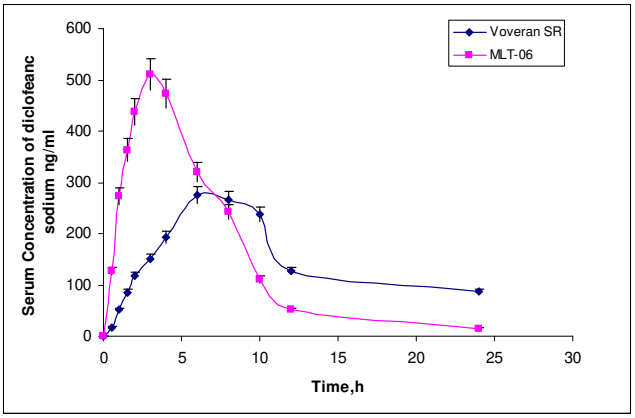

Figure 2. Profile of mean serum concentration versus time of diclofenac sodium in healthy human volunteers (n=8).

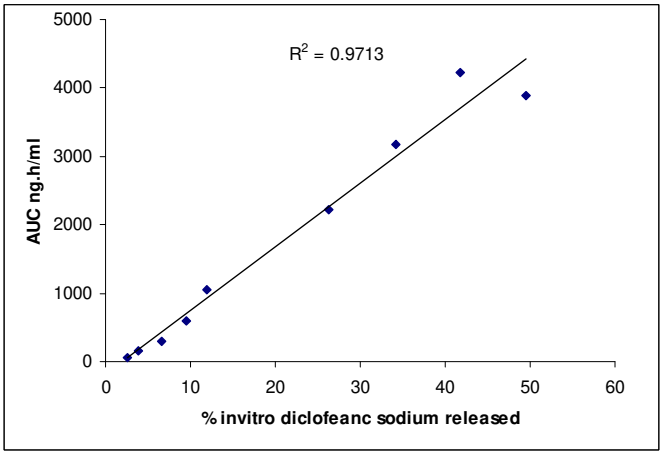

Figure 3. IVIVC of layered matrix tablets MLT-06.

The serum concentrations of diclofenac sodium at different time intervals following oral administration of both the formulations (Voveran SR and MLT-06) (figure 2). The mean pharmacokinetics parameter of diclofenac sodium is shown in table 2**.** The peak serum concentration (C_{max}) and time to reach peak concentration (T_{max}) of Voveran SR and MLT-06 were found to be 553.75ng/ml (±21.88), 3.43hrs (±0.67) and 275.48ng/ml (±5.40), 6.00hrs (±0.00) respectively. $AUC_{0-\infty}$ for Voveran SR and MLT-06 were found to be 3789.84ng/ml/h (±29.62) and 4997.09ng/ml/h (±341.16) respectively. The lower C_{max} of formulation MLT-06, prolonged the T_{max}. Mean residence times (MRT) of Voveran SR and MLT-06 formulation were 8.16hrs and 12.72 hrs. A significant difference ($P<0.05$) was observed for the time to reach peak concentration T_{max} and Mean residence time (MRT) between these two formulations. Thus lower C_{max} of MLT -06, prolonged T_{max}, and increase in $AUC_{0-\infty}$ shows unaltered bioavailability. It indicated that release of diclofenac sodium from MLT-06 formulation is slow and it may be attributed due to the longer residence time in the GIT, there by providing a controlled and effective absorption of diclofenac sodium. In vitro-In vivo correlation was done by plotting percentage drug absorbed versus in vitro drug release. The plot was linear for the layered matrix tablet (MLT-06) with a correlation coefficient of 0.913, indicating high correlation (figure3). This in vitro-in vivo correlation is of great use in developing controlled release tablets [11].

Conclusion

The layered matrix tablets (MLT-06) can be a useful alternative formulation in comparison with matrix type Voveran SR tablet. It was observed that Voveran SR tablets could n't with stand GI movements and released the diclofenac sodium quickly with in 3hrs, resulting in faster absorption. There by it produces high peak concentration C_{max} with earlier T_{max}, when compared to layered matrix MLT-06. Guar Gum

dispersed matrix core layered with 75mg of Na CMC on both the surfaces as barrier layers were found to be useful to achieve controlled release of diclofenac sodium through out the gastrointestinal tract.

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