DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE DICLOFENAC SODIUM MATRIX TABLETS

By

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Dedication

Dedicated To my parents, my small family

(My Wife, my children)

and to Dr. Hussein Mustafa Ali

who encouraged me to

complete my study

Acknowledgement

All my praises and thanks to Almighty AllA the lord of all Universe for his help to complete all this work. My thanks and gratitude to my supervisory team Dr. Abdulkarim Mohmed Abdulkarim and Dr. Elamin Ibrahim Elnima for their supervision, guidance reviews and fruitful discussion ,which enabled me to finish this work at the stated time.

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Abstract

In vitro release profiles were studied for the matrix controlled release Diclofenac sodium tablets (MT20, MT33, MT34) in comparison with Voltaren retard (V.R) a well known marketed Diclofenac sodium controlled release tablets from *Novartis® (Switzerland)*. Percentage release of Diclofenac sodium was studied in gradient pHS (1.2, 2.1, 4.2, 5.5, 6.5, 6.7, & 7.2) in accordance with gastric pHS, which are varying from pH one to eight. The study included the release profiles and evaluated the kinetics of diffusion and diffusion exponents.

Analysis of new controlled release oral drug delivery systems using, C8 (Eurosphere-100 (5 μm) 4.6 mm ID x 250 mm) and C18 (Eurosphere-100 (5 μm) 4 mm ID x 100 mm) columns was carried out. The mobile phase was phosphate buffer/methanol. Spectrophotometric detection was at 272 nm. Percentages of content for the different matrices were evaluated.

Based on t-test no significant difference was found between content measurements using C8 and C18 columns at p′-value of 0.05. (Observed t-value was 0.062 compared to the theoretical value of 2.15. Content analysis showed good precision and accuracy with C8 rather than C18.

In vivo performance and bio-equivalence of controlled release matrix tablets (MT33) containing gum Arabic and Guar gum was compared to a standard control drug Voltaren retard in healthy male volunteers.

The study design was randomized cross-over study. Blood samples were collected at pre-determined periods, up to 12 hours and one sample was taken after 24 hours.

High performance liquid chromatographic (HPLC) analysis was done for both sample and control. Parameters such as $C_{max,}$ T_{max}, AUC_{0-24},

K_{el} and MRT_{0-24}. $AUMC_{0-t}$, $AUMC_{0-\infty}$ were obtained. The bio-equivalence of both formulations was evaluated which showed no difference in prolonged action in vivo performance between controlled matrix tablets (MT33) containing gum Arabic and guar gum compared to a standard control drug ; Voltaren retard in healthy volunteers.

Accelerated stability study for six months was performed for controlled release matrix tablets (MT20, MT33, MT34, MT33p, MT34p) containing natural gums (gum Arabic, guar gum), semi-synthetic gum (Xanthan gum), Eudragit L100 (methacrylic acid and methyl methacrylate), and Hydroxypropylmethylcellulose.

Microbiological tests for matrices were evaluated by comparing preserved and non preserved tablets. Content was found to be 90-105% in all the five matrix formulae. Applying out of trend stability rules (OOT), the best formula was MT33 which contain guar gum 15% and gum Arabic 15%. No changes in physical appearance and organoleptic properties were observed. No microbiological growth (bacteria or fungi) was observed in both preserved and non-preserved controlled release formulae.

بسم الله الرحمن الرحيم

الملخص العربي للدراسة

تهدف هذه الدراسة لإيجاد تقنية جديدة بأستعمال الصمغ العربى وصمغ القوار لإيجاد نسيج ضام مناسب لإنتاج مستحضر الدايكلوفيناك صوديوم 100 ملجم ذو المفعول الطويل وهو احد مسكنات الألم الشائعة . وقد تم تحضير عينات من هذه المستحضرات باستعمال الصمغ العربي وصمغ القوار وصمغ الاكزنتان وهيدروكسي بر وبيل مثيل سيللوز والايدراجيت ل 100 .

وباستعمال طرق التحليل المختلفه تمت دراسة تحرر الدايكلوفيناك صوديوم في هذه المستحضرات في وسائط ذات درجات حمضيه وقاعدية وشبه متعادلة مماثلة لتلك التي توجد في قناة الجهاز الهضمي . ومقارنة هذه المستحضرات مع مستحضر قياسي هو فولتارين ريتارد (سويسرى المنشأ) .باستعمال جهاز الذوبان وفق طرق دستور الأدوية البريطانى والأمريكى. كما شملت الدراسة حركية الانتشار لهذه المستحضرات .

شملت هذه الدراسة تحليل هذه المستحضرات باستعمال جهاز كروماتوغرافيا السائل ذو الضغط العالي باستعمال عمودي فصل س 18 وس 8 ومحلول فصل محدد متعادل الفوسفات بتركيز هيدروجيني 2.5 (34 حجم) ميثانول (66 حجم) وتمت مقارنة هاتين الطريقتين باستعمال طرق إحصائية محددة .

كما تمت دراسة ثبات سريعة (ستة اشهر) لهذه المركبات في درجة حرارة ورطوبة قياسية (40 درجه مئوية و 75% رطوبة نسبيه) .

وشملت الدراسة كل الأقراص التي تحتوى على صموغ ومواد حافظة لمعرفة مدى وجود تلوث أو بكتريا فى هذه المستحضرات . وتم تقييم نمو الباكتريا والفطريات في هذه العينات باستعمال وسائط مناسبة. وبعد ستة أشهر من الدراسة المستمرة لم يتم الحصول على ملوثات الباكتريا والفطريات وخلو المستحضرات من الباكتريا الممرضة. مما يعزز فكرة أستعمال هذه الصموغ فى المستحضرات الصيدلانية الجافة.

كذلك اجريت دراسة التكافؤ الحيوي للمركب النهائي MT 33 ومقارنته مع مركب قياسي هو فولتارين ريتارد في عينات من المتطوعين (عدد 12) تم اخذ عينات من الدم كل ساعة ولمدة 24 ساعة . وفصل البلازما وتحليل نسبة تركيز الدواء فى البلازما خلال فترة الدراسة . وحساب المقاييس الحركية للدواء وفق طرق إحصائية محددة . وبمقارنة المستحضر MT 33 مع المستحضر القياسي فولتارين ريتارد وجد بأنه ليس هنالك فرق ذو قيمه بين المستحضرين باستعمال طرق التباين الإحصائية مما يؤكد جودة المنتج وفعاليته .

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Abbreviations

A	=	Drug loading per unit volume
A	=	Frequency factor
ANOVA	=	Analysis of variance
Aex	=	Concentration of water soluble excipients
AUMCo-24	=	Area under the carve from zero time to 24 hours
AUMCt	=	Area under the moment carve at time t
AUC∞	=	Area under the carve at time infinity
AUC	=	Area under the curve
C	=	Concentration
C1 and C2	=	Concentration (reading) one and two
Cmax	=	Maximum blood concentration
C8	=	Silica column (Microphere100) length 25cm x 4.6mm diameter
C18	=	Silica column (Microphere100) length 10 cm X 4.0 mm diameter
Cs	=	Solubility
ΔC	=	Concentration gradient
C last	=	Last concentration
CAP	=	Coating by acetate phthalate
CMC	=	Carboxy-methyl-cellulose
Cox	=	Cyclo-oxygenase(one and two)
CPM	=	Carboxy-poly-methylene
CPMP	=	Committee for proprietary medical products
D	=	Diffusion coefficient in matrix phase
D	=	Dose
Da	=	Diffusion coefficient in aqueous phase
DC	=	Direct compression

d Mt/dt	=	Steady state release rate
dV/dT	=	Rate of water flow
ϵ	=	Porosity
ϵa	=	Initial porosity
ϵd	=	Porosity created by extracting the drug
ϵex	=	Porosity due to water soluble excipients
EOP	=	Elementary osmotic pressure
GIT	=	Gastrointestind test
H	=	Activation energy
hr	=	Hours (s)
HEC	=	Hydroxy-ethyl cellulose
HPC	=	Hydroxy propyl cellulose
HPLC	=	High performance liquid chromatography
HPMC	=	Hydroxy-propyl- cellulose
HPMCP	=	Hydroxy – propyl -methyl-cellulose phthalate
ICH	=	International conference for harmonization
IND	=	Investigational new drug application
IVIVC	=	In vitro in vivo
J	=	Tortuosity
K	=	Elimination rate constant or partition coefficient
K_1 and K_2	=	Constants
K	=	Constant
k	=	Hydraulic permeability
K_{el}	=	Elimination rate constant
L	=	Diffusion path length
Ln	=	Logarithmic
LOD	=	Limit of detection
Mm	=	Millimeter

MC	=	Methyl-cellulose
Mg	=	Milligrams
ML	=	Millie - liter
mAU	=	Milliamp unit (peak area)
MEC	=	Minimum effective concentration
MT	=	Total amount of drug released at time t
MT20	=	Matrix tablet NO 20
MT33	=	Matrix tablet NO 33
MT34	=	Matrix tablet NO 34
MT33P	=	Preserved matrix tablet NO 33
MT34P	=	Preserved matrix tablet NO 34
$MT/MT\infty$	=	Fraction released
MTR	=	Mean residence constant
n	=	Diffusion exponent
N	=	Number of subject
NF	=	National formulary
NDA	=	New drug application
NS	=	Non significant
OOT	=	Out of trend
P	=	Drug density
P-Value	=	analysis of variance
ΔP	=	Hydrostatic pressure difference
Pex	=	Density of water soluble excipients
PEO	=	Poly-ethylene oxide
PVA	=	Poly-vinyl-acetate
PVC	=	Poly-vinyl-chloride
Q	=	Fraction of drug released at time t
Q60	=	Quantity of dissolved drug (60%)

R	=	gas constant 1.987 cal deg^{-1} mol^{-1}
r	=	Correlation
R & D	=	Research and development
RSD	=	Relative standard deviation
S	=	Effective membrane surface area of drug diffusion
[S]	=	Solubility
SD	=	Standard Deviation
Sig.	=	Significance of different
STD	=	Standard diclofenec sodium
SGOT	=	Serum glutamate paruvate trans-aminase
SGPT	=	Serum glutamate oxalo- acetate trans-aminase
T	=	Absolute temperature
t	=	Time
T_{max}	=	Time to reach the maximum concentration
T_{50}	=	Time required to dissolve 50% of drug
$t_{½}$	=	Half time
T_1 and T_2	=	Time one and time two
USP	=	United states pharmacopoeia
V/V	=	Volume by volume
VR	=	Voltaren retard
W/V	=	Weight by volume
WHO	=	World health organization
$\Delta\pi$	=	Osmotic pressure difference
***	=	Mean values represent the mean of 6 subjects taking Voltaren retard plus 6 subjects taking MT33
**	=	P-value of the analysis of variance
N*	=	No of subjects
Min.	=	Minutes

Chapter I

1.1 Introduction and literature review

Controlled release formulation is to give a drug at predetermined rate, maintaining a constant drug level in the body for longer period, with concomitant minimizing of undesirable side effects (1).

Solid matrix controlled release is usually prepared by incorporation of a drug into a bed, with physical or chemical properties to release a drug in a prolonged plateau release pattern, attaining the minimum effective concentration (MEC). Due to the easiness, effectiveness, and economically feasible matrix formulations the research and development (R&D) scientists in pharmaceutical area recently search for new controlled matrices with zero- order release kinetics. The controlled release systems were classified according to the mechanism of transport as diffusion controlled, swelling controlled and chemically controlled systems. The objectives of controlled release systems design is to predict the release, elucidate the transport through mathematical models, design the delivery system and optimize the release kinetics (2).

1.2 Fundamental concepts in controlled release:

In controlled release formulations, the fate of the drug may be characterized by a single compartment, which is described by the plasma concentration of drug with time. The concentration of drug at receptor site versus time reflects the pharmacodynamics or biological response, whether it is related to efficacy or adverse reaction. On addition of more drugs, the steady state of equilibrium was reached between the plasma and the receptor.

In controlled release, drug involves the application of physical and polymer chemistry to produce a reproducible dosage form to control the entry of drug with a required profile.

The delivery rates of controlled release systems may be characterized by kinetics of drug and physical processes. A zero-order in which the release is constant with time is the ideal one.

The zero-order release involves the diffusion through semi-permeable membrane. The membrane is initially loaded with drug to obtain an initial burst and followed by steady state diffusion.

1.3 Oral controlled release dosage forms

Typical control release is designed to provide constant or nearly constant drug levels in plasma with reduced fluctuation via slow release of drug over an extended period of time. Controlled release should reduce dosing frequency compared to the conventional dosage form (2).

The common oral polymeric controlled releases are matrix, membrane controlled and osmotic systems. The mechanism of polymeric controlled release dosage forms involves drug diffusion though viscous gel layer, tortuous channels, or a barrier-drug dissolution via system erosion, and drug solution via osmotic pressure.

Oral controlled polymeric systems include matrix, reservoir, and osmotic systems.

The matrix systems include:

1. Hydrophilic, matrix.
    - Swellable.
    - Swellable and erodable.
2. Hydrophobic matrix
    - Homogeneous (non porous).
    - Heterogeneous (porous).
        i. Inert (monolithic)
        ii. Erodable.
        iii. Degradable.

3. Reservoir systems :
    - Coated beads or pellets
    - Micro-encapsulation.
4. Osmotic systems
    - Elementary osmotic pumps.
    - Push-pull system.
    - Push-layer system.
    - Push-stuck system.
5. Bio-adhesive and buoyant formulations.

In matrix system the drug is incorporated into the polymer matrix by either particle or molecular dispersion (by dissolution).

In hydrophilic matrix there are two competing mechanisms involved in the drug release, Fickian and relaxational release. Not only diffusion affects drug release in controlled release from hydrophilic matrices, but the erosion followed by polymer relaxation contributes to the process of release.

Drug release behaviour from hydrophilic matrix was expressed by a simple semi- empirical formula (58).

$Q = Kt^n$

Where Q = fraction of drug released at time t.

K= rate constant related to the characteristics of macromolecule network and drug, and n is the diffusion exponent. The value of n was indicative of drug release mechanism. For n = 0.5 drug release followed Fickian diffusion, which is driven by a chemical potential gradient.

For n = 1 drug release occurs via relaxational transport associated with stresses and phase transition in hydrated polymers. For $1 > n > 0.5$ non Fickian diffusion results from diffusion and polymer erosion.

In relaxation transport in Donald. L (2) reported (Peppas and Sahlin) following equation:

$$Q = K_1 t^n + K_2 t^{2n}$$

where K_1 and K_2 are constants reflecting the relative contribution of Fickian and relaxational mechanisms. When the surface area is constant (fixed) the value of n should be 0.5 and hence.

$$Q = K_1 t^{0.5} + K_2 t$$

The above equation described the release from hydrophilic matrices.

In hydrophobic inert matrix the drug is dispersed throughout the matrix. In homogeneous monolithic matrix the release behaviour was described by Higuishi equation subject to matrix boundary conditions (2).

$$M_t = [D\ Cs\ (2A - C\ s)\ t]^{½}$$

Where Mt = drug released per unit area at time t.

A = drug loading per unit volume.

Cs = solubility

D = Diffusion coefficient in the matrix phase.

The above equation was valid on the assumptions:

a) A pseudo-steady state exists.

b) Drug particles are small compared to the average distance of diffusion.

c) Diffusion coefficient is constant.

d) Perfect sink condition exists in the external media

e) Only the diffusion process exists.

f) Drug concentration in the matrix is greater than solubility in the polymer.

g) No interactions between drug & matrix.

When A » Cs the above equation was reduced to

$M_t = [2D\ AC\ st]^{½}$ and thus the amount of drug released is proportional to the square root of time, A, D, & Cs.

Release from porous monolithic matrix systems, involves penetration of surrounding liquid, dissolution of drug and leaching of

drug through the interstitial channels or pores. Volume of channels or pores and length of openings in the diffusion process leading to Higuishi equation, Donald (2), which is as follows:

$$M_t = \left(\epsilon Cs\ (2A - \epsilon Cs)\ \frac{Da}{J}\ t \right)^{1/2}$$

Where ϵ and J are the porosity and tortosity of the matrix respectively. Da is the diffusion coefficient in aqueous phase. When (A » C s).

$$Mt = (2Da\ ACs\ \frac{t}{J}\ t)^{1/2}$$

The porosity ϵ is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate. It is the total porosity after the drug has been extracted. It consists of the initial porosity, ϵ a , due to air or void space in the matrix before the leaching process begins and the porosity created by extracting the drug ϵ d, and water soluble excipients ϵ ex.

$$\epsilon = \epsilon\ a + \epsilon\ d + \epsilon\ ex = \epsilon\ a + \frac{A}{\rho} + \frac{Aext}{\rho\ ex}$$

Where ρ is the drug density and ρex and Aex are the density and concentration of water soluble exciepents respectively.

When no water soluble exciepent was used:

$$\epsilon = \epsilon\ d = \frac{A}{P}$$

And hence

$$Mt = A \left((2 - \frac{Cs}{\rho})\ \frac{Da\ Cs}{J\rho}\ t \right)^{1/2}$$

$$Mt = A\ (2Da\ \frac{Cs}{J\rho}\ t)^{1/2}$$

In a porous monolithic matrix the release is directly proportional to the matrix A.

Ritger and Peppas derived the following equation. Donald reported it, (2) proposing the general release behaviour from hydrophobic matrices in the form of slab, sphere and cylinder. As tablets were considered as short cylinders, the drug released was calculated from:

$$Q = Kt^n$$

Q = is the fraction released

K = is constant

N = diffusion exponent

In the case of Fickian release the exponent n has value 0.5 for slab, 0.45 for sphere & 0.43-0.05 for cylinders .In reservoir polymeric systems the common methods for reservoir polymeric system are:

- Micro-encapsulation of drug particles.
- Coating of tablets or multi particles.
- Press coating of tablets.

A polymeric membrane makes resistance to drug diffusion from the reservoir to the sink. Usually the driving force is the concentration gradient of active molecules between reservoir and sink .The resistance provided by the membrane is the function of film thickness and characteristics of both the film and the migrating species in a given environment. The modern method of drug release from the film coated dosage forms may be categorized into:

- Transport of the drug through a network of capillaries filled with dissolution media.
- Transport of the drug through a hydrated swollen film.
- Transport of a drug through, flaws, crack, and imperfections within the coating matrix.

Based on Ficks first law of diffusion the release rate of the drug from the recovered polymeric system at steady state is given by the following equation.

$$\frac{dMt}{dt} = \frac{DSK}{L} \triangle C$$

Where Mt is the total amount of drug released at time t.

D is the diffusion coefficient of the drug.

S is the effective membrane or barrier surface area of drug diffusion.

L is the diffusion path length (thickness of the film).

K is partition coefficient of drug between the barrier and aqueous phase

$\triangle C$ is the concentration gradient.

In case where D, S, K, L & $\triangle C$ are constants. The amount of drug released as a function of time can be obtained by the following equation.

$$Mt = \frac{(DSK\ AC)t}{L} = Kt$$

Where K = the release rate constant.

In osmotic pump systems a tablet core is encased by a semi – permeable membrane with an orifice. When the system is exposed to body fluid, water will migrate through the semi- permeable membrane into the tablet core containing osmotic exciepents and active drug. There are usually two osmotic pumps used.

1. One chamber elementary osmotic pump (EOP).
2. Two chambers system (e.g. push-pull)

In both systems the rate of water penetration into the systems in terms of volume can be expressed by:

$$\frac{dV}{dt} = \frac{Ak}{L}(\triangle\pi - \triangle P)$$

Where $\frac{dV}{dt}$ = rate of water flow

K is the hydraulic permeability

A is the membrane area

L is the thickness

$\triangle \pi$ is the osmotic pressure difference

$\triangle P$ is the hydrostatic pressure difference.

Due to rigidity of device the volume of the device is constant during operation and the amount of drug released at time t is:

$$\frac{dM}{dt} = \frac{dV}{dt}[S]$$

Where [s] is the drug solubility (2)

When the hydrostatic pressure difference is negligible

$$\frac{dM}{dt} = \frac{kA}{L}\triangle\pi[S]$$

Another system includes ion exchange which contains resins composed of water-insoluble cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchange with appropriate charged ions that are in contact with the ion exchange groups.

1.4 Materials used for control drug release.

Materials used for controlled release are divided according to the application used into:

- Matrix
- Reservoir
- Osmotic pumps.

1.5 Matrices in controlled release drugs:

They include hydroxylpropylmethylcellulose (HPMC), hydroxylethylcellulose (HEC), Xantham gum, sodium alginate polyethylene oxide, cross-linked homopolymers and co- polymers of acrylic acid supplied in micronized forms. HPMC grades are classified according to the viscosity of 2 % solution, which ranges from 100 to 100.000 cps. Insoluble resins as carpobols were also used.

1.6 Materials used for reservoir systems.

They include, water insoluble acrylic copolymers and ethylcellulose. They are used in organic solutions but recently used as aqueous dispersions (2).

The acrylic and meth–acrylic acid derivatives include the Edragits.

Ethylcellulose for film coating available as an aqueous polymeric dispersion containing plasticizers was used under the brand name of surelease (colorcon) and pseudo - latex dispersion.

Coating by acetate phthalate (CAP) hydroxylpropyl-methylcellulose phthalate (HPMCP), Eudragit L & S, are all pH–dependent .They dissolve at pH > 5.5 leading to release of drug at the intestine avoiding the stomach (pH = 1.2) .

Polymers used for Osmotic pump systems, include cellulose acetate containing certain percentage of acetyl content .They are used together with other pH-dependent and pH-independent cellulose derivatives to form a semi-permeable membrane. Other polymers include polyurethane ethylcellulose, poly (ethyl oxide) polymers, polyvinylchloride (PVC) and poly vinyl acetate (PVA).

1.7 Technologies used for oral controlled systems:

Oral controlled release systems are in the form of tablets and capsules. The technologies used for tablet dosage forms were,

spheronization (or pelletization) and film coating of single unit or multi-particulates.

1.7.1 Tablet process technology:

This technology includes conventional processes of granulation, blending, compression and coating. In matrix technologies the pre-compression is needed because high concentrations of polymers are often used (2).

1.7.2 Spheronization (pelletization) process technology.

It is done by using microcrystalline cellulose. Pellets or beads or spheres were produced, since they minimize the process of dose dumping. Usually these pellets or beads have different release rates .The basic method of pellets or beads formation include:

a) Micro-encapsulation.

b) Spray congealing.

c) Formation of particles from plastic mass.

d) Agglomeration.

1.7.3 Coating technology:

Coating is by deposition of a uniform membrane of polymer onto the surface of substrate as tablet, spheres, pellets, and drug particles.

Coating process technology includes:

- Film coating.
- Layer coating.
- Compressed coating.

The properties of the coating are the function of coating formulation as well as coating process variables.

The equipment used is either coating pan, fluid bed or a rotary granulator.

1.8 Feasibility assessment of controlled release.

The feasibility is not economically but rather therapeutically dictated by the following parameters as: (2)

- Physicochemical.
- Biopharmaceutical.
- Therapeutic.
- Overcome physiological constrains.

1.9 The most important factors in controlled release are:

1.9.1 Solubility:

Poorly soluble drugs are usually extended in action due to the slow dissolution. However the dissolution kinetics of these drugs is non-linear and varies with particle size, surface area, and size distribution. The absorption is also extended since the amount of fluid available for dissolution is limited.

1.9.2 Stability:

Drugs must be stable to pH, enzymes, and flora, through the gastro-intestinal tract (G.I.T).

1.9.3 Lipophilicity / Permeability:

Absorption of hydrophilic drugs with poor permeability may be limited by membrane permeation which varies with the surface area and enzymatic activities in different regions of GIT. Changing the release rate of such drugs may have little effect on the shape of plasma profiles and may even result in deceased absorption (2).

1.9.4 Elimination t½:

The philosophy behind the controlled release is the extension of the short half life of drugs (2- 6 hr) to longer half life but other factors as minimum effective concentration (MEC) , volume of distribution and dose, determine the feasibility of controlled release drug .

Controlled release may be feasible with one drug while it may be non feasible with other drugs of the same half life.

1.9.5 Therapeutic window:

The most important criterion of controlled release is the ability to maintain plasma levels within therapeutic range with reduced fluctuations. For drugs with relatively short half–lives, the lower the minimum effective concentration (MEC) is, the more likely it is to achieve prolonged drug exposure above MEC with controlled release systems, but with fluctuations of plasma level at steady state. This is undesirable in narrow therapeutic-index drugs.

1.9.6 First pass metabolism:

Drugs with saturable first pass metabolism (hepatic or gut), bio-availability will be decreased due to the systemic input from controlled release systems limiting the chance of success.

1.9.7 Pharmacokinetic, pharmacodynamic relationship (PK/PD) relationships:

Relationship between drug concentration (C) and pharmacological effect (E) is described by a sigmoid E max model. A shallow E-C relationship indicates a slight response E in high concentration which gives no rational controlled release development (2).

Controlled release of drugs is to release a drug at specific target, to act either systemically or locally. The objective of controlled release of drugs is to modify the normal behavior of drugs molecules in a physiological environment. It can lead to the followings:

1- Sustained drug action at a predetermined rate by maintaining a constant effective drug level in the body with concomitant minimizing of undesirable side effects associated with a saw tooth kinetic pattern. This will give a constant drug release at specific

period of time attaining a constant blood level. More specifically it is a modification of drug that prolongs its therapeutic activity (2).

2- Localization of drug action in the diseased tissue or organ, to avoid the activity of drug at specific target due to its untoward properties.

3- Targeting drug action by a carrier to deliver drug to a particular target (3).

Locally acting drugs sometimes target a specific part of gastro-intestinal tract (G.I.T). Metronidazole and Albendazole drugs were incorporated in guar gum to give a colon targeted formulation (4).

Oral controlled release dosage forms are developed to specific targets with improvement of pharmacological action and reduced toxic side effects (5). Despite of overcoming patient's compliance by controlled release formulations; new technology development in tablet production is established. The decrease of incidence of adverse drug reaction is also achieved.

Hydrophilic matrices containing swelling polymers are referred to as hydro gel matrices; swelling controlled release systems or hydrophilic matrix tablets (6). A number of polymers have been investigated for development of in situ gel forming systems due to their ability to control the release of drug from aqueous media due to its physical property of swelling or cross-linking (7, 8, 9).

Hydrophilic matrices include: carboxymethylcellulose sodium (CMC), methylcellulose (MC), hydroxypropylcellulose (HPC), and hydroxyethylcellulose (HEC), polyethylene oxide (PEO), polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), carboxypolymethylene (CPM), alginic acid, gelatin and natural gums (10). These matrices can be formed into a tablet by direct compression or wet granulation containing the active drug with the hydrophilic matrix.

Various designations for controlled release drugs are called: Smart, Targeted, Intelligent, Novel and Therapeutic controlled release dosage forms.

Most of the controlled release systems fall in the category of passive programmed, in which the release is pre-determined and is irresponsive to the eternal biological environment.

Controlled release dosage forms also reduce fluctuations in plasma drug level by slowing down the absorption rate due to slower drug release from the system.

Enteric coated formulations comes under the category of controlled delivery systems in which the release of drug in the stomach is avoided and release of drug takes place in the intestinal region for absorption. Polymers have gained an important role in the pharmaceutical industry as drug encapsulates and vehicles of drug carriage protecting or controlling the drug release (11).

1.10 Advantages of controlled release:

A- Delivery to the required site.

B- Delivery at the required rate.

C- Reduce the danger of overdose or side effects.

D- More efficient dosage.

E- Reduce dose frequency.

F- Reduce fluctuations in circulating drug level.

G- Decrease patient compliance.

H- Avoidance of night- time dosing.

I- More uniform effect.

J- Reduction of GIT irritations.

1.11 Disadvantages of Controlled release Drugs:

A- Cost is very high. The high cost of controlled release dosage forms must again be taken into account when the advantages and

disadvantages of the drug formulated in controlled release manner is being considered.

B- Unpredictable in vitro in vivo correlation. Dose dumping (12) is a phenomenon whereby large quantity of medication in a controlled release formulation is rapidly released introducing potentially toxic quantities of drug into systemic circulation. This has been reported for vasodilators. Reduced drug absorption is an intrinsic hazard since the dose is partially released at the stomach especially in matrix controlled release drugs. And apart from the gastric residence time this fraction of released drug is at a distal region to the optimum absorptive region of the intestine which is considered as absorption window and may give rise to unsatisfactory drug absorption in vivo despite the excellent release characteristics for in vitro.

C- Dose dumping, because sometimes controlled release dose is 16 times the normal dose which may cause toxic side effects if chewed.

D- Reduced potential for dosage adjustment and increased potential for 1st pass clearance and hence poor availability. Reduced potential for dosage adjustment is a major disadvantage of some controlled release products. And this should be considered when preparing controlled release formulations.

Reduced potential for dosage adjustment is a major disadvantage of some controlled release products. And this should be considered when preparing controlled release formulations. Hepatic metabolism is a saturable process. After oral dose the drug reaches the liver via the portal vein in far greater concentrations than normally observed in systemic circulation. In fact the levels may be high enough to exceed the capacity of hepatic metabolizing

enzymes. Thus the higher the oral dose the greater is the possibility of saturating hepatic drug metabolizing enzymes. Conversely the smaller the dose or slower the release of the drug from the formulation, the smaller is the possibility of saturating fist pass metabolism. The potential for reduced drug availability due to first pass metabolism is therefore greater with controlled release formulations than with conventional dosage forms. Hepatic metabolism is a saturable process. After oral dose the drug reaches the liver via the portal vein in far greater concentrations than normally observed in systemic circulation. In fact the levels may be high enough to exceed the capacity of hepatic metabolizing enzymes. Thus the higher the oral dose the greater is the possibility of saturating hepatic drug metabolizing enzymes. Conversely the smaller the dose or slower the release of the drug from the formulation, the smaller is the possibility of saturating fist pass metabolism. The potential for reduced drug availability due to first pass metabolism is therefore greater with controlled release formulations than with conventional dosage forms.

E- Effective drug release is affected by gastro intestinal residence time.

1.12 Controlled release Input factors:

A- A sound development / design manufacture base.

B- Pre-formulation research data.

C- Rational dosage form design.

D- Formulation of reliable and stable system.

E- A precise, reproducible manufacturing scheme.

F- A sensitive product quality control.

G- Qualified and responsible personnel in management and, R&D, quality control, production, and services (12).

1.13 Controlled release drugs outputs:

A- Effectiveness.

B- Safety.

C- Reliability and stability.

D- Pharmaceutical elegance.

E- Appearance and organoleptic properties.

F- Convenience.

G- Ease of use.

H- Dosing frequency.

I- Consumer acceptance.

1.14 Evaluation of controlled release preparations:

1.14.1In vitro

A- Dissolution rates.

B- Tablet hardness for polymer matrix.

C- Porosity of tablets.

D- Weight variations.

E- Content uniformity.

F- Friability.

1.14.2 In vivo

A- Pharmacological response.

B- Clinical response.

C- Blood level data C_{max}, $t_{1/2}$ AUC.

D- Urinary excretion.

E- Kinetic studies according to 1^{st}, Zero, or Higuishi equations.

F- Toxicity studies.

1.15 Regulatory Assessment:

Demonstration of safety and efficacy of controlled release drugs by (13).

A- Controlled clinical studies required to demonstrate the safety of and efficacy of the drug in controlled release formulation.

B- Drugs that are approved to be safe in controlled release forms, data are required to establish bio-availability compared to an approved controlled release product of the same origin.

C- A single dose bio-availability is necessary and acceptable in case of study the amount of absorbed, in fasting.

D- No dose dumping.

E- The formulation of controlled release should provide consistent pharmacokinetics performance between individual forms.

F- In vitro and in vivo methods should be correlated in controlled release products.

1.16 Fabrication techniques:

There are different methods of fabrication of controlled release drugs by:

A- Increasing of the particle size of the drug.

B- Embedding the drug in a matrix.

C- Coating.

D- By dry complexes.

E- Using ion exchange resin.

Matrix tablets for controlled release were supposed to have superior benefits to the other methods of preparation. Direct compression (DC) method is time saving less labor, non-tedious, with less machinery required. This will save money and time. One method of formulating controlled release tablets is by incorporation of a drug in a hydrophilic matrix which controls the rate of release (14, 15). The use of HPMC was illustrated in mathematical models as controlled release matrices (16).

Sustained release tablets are made by incorporation of natural and/or synthetic polymers to import the sustained release property to the

formulation. The polymers are: Wax matrices, Hydrogenated oils, fatty acids and alcohols esters of fatty acids, Metallic soaps; which all act as coat or entrap to limit the solubility of the drug and prolong its release. Slightly soluble drugs are more susceptible to prolonged action to provide drug level within the therapeutic range 8-12 hours with a single dose rather than a short action. This prolonged release is affected by gastric motility whether delayed or enhanced since the gastro-intestinal tract motility is not uniform.

1.17 Matrix tablet formulation:

Several hydrophilic patented matrices have been in use as synchron technology (17) and hydrodynamically balanced systems (18). Addition of water to hydrophilic matrix activates the release of drug. The formation of hydrophilic base gel layer around the tablet after immersion in water makes controlled release, which is effective by gel diffusion barriers to control erosion of tablets (10).

Acacia alone as a prolonged release matrix was found to be ineffective as a controlled release matrix which was due to short chain molecules of acacia. The three layer matrix tablet also showed no controlled release. A combination of gum Arabic and guar gum was found to be of similar controlled action as the polysaccharide blend of guar gum and naturally occurring gums as gum Arabic.

The effect of formulation and drug release behavior from different hydrophilic matrices can be summarized in the following points.

The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An adequate polymer hydration rates my cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water.

The amount of hydrophilic polymer in tablet formulations was reported to have a marked influence on the disintegration time and dissolution of the tablet. The disintegration time was extended as polymer content increased. The release rate of drug was decreased when the proportion of polymer was increased but differed quantitatively with different drugs and different matrix building materials. Slower hydration polymers can be used at higher concentration level to accelerate gel formation or reserved for water insoluble drug (s).

Generally reduced particle size of hydrophilic polymer ensures rapid hydration and gel formation, leading to good controlled release .The impact of polymer particle size on the release rate is formulation dependant, but may be obscured in some cases. The particle size of a drug, within a normal size range, my not significantly influence the drug release from the matrix tablet. Extremes of drug particle size may affect release rate of the drug.

Viscosity characteristics of the polymers are of real importance in determining the final release properties of the matrix tablet. Generally the drug release rate is slower for a higher viscosity grade polymer.

Commonly water soluble excipients in the matrix tablets can increase drug release. However, addition of water soluble materials may achieve slower rate by increasing viscosity of the gel through interaction with hydrophilic polymers or by competition with matrix materials for water. When water insoluble non-swellable excipient(s) or drug(s) is used in the matrix system stress cracks can occur upon immersion in water because of the combination of swelling or non-swelling components on the tablet surface.

For some hydrophilic matrix building materials, pH may affect the viscosity of the gel which forms on the tablet surface and its subsequent rate of hydration. Under acidic conditions carboxypolymethylene and

Sodium carboxymethylcellulose have little or no retarding effect on the drug release rate. Gelatin forms gels of higher viscosity in acidic media and is more effective in retarding drug release as compared to basic media.

No conclusions have been drawn from the effect of compression force on drug-release behavior in hydrophilic matrix materials. However, tablet size and shape can significantly influence the drug-release kinetics.

The drug can be incorporated into fat-wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactants, and spray-drying techniques. In the bulk congealing method a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy material(s), and filler(s) also can be converted into granules by compacting with a roller compacter, heating into a suitable mixer such as a fluidized-bed and steam-jacketed blender, or granulating with a solution of waxy material or other binders. Fat-wax granulations containing drug obtained from all of the above processes may be compressed to form tablet cores or directly compressed to a final tablet form with sustained release properties.

The drug embedded into a melt of fats and waxes is released by leaching and / or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastro-intestinal tract. Enteric materials such as cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylate copolymer, Zien and shellac may be used to prepare matrix tablets with somewhat a similar drug-release mechanism. In general the primary constituents of fat wax matrix are fatty acids and /or fatty esters. Fatty acids are more soluble in an alkaline rather than an acidic medium. Fatty esters are more susceptible to alkaline catalysed hydrolysis than to acidic catalysed hydrolysis. The surface erosion of a fat-wax matrix

depends upon the nature and percent of fat-wax and extenders in a matrix. Other factors such as drug particle size and drug concentration affect release of the drug from the matrix system. The addition of surfactants to the formulation can also influence the drug release rate and the proportion of the total drug incorporated into a matrix. Polyethylene, ethylcellulose, and glycerylesters of hydrogenated resins have been added to modify the drug-release pattern.

Sustained-release tablets based upon an inert compressed plastic matrix were first introduced in 1960 and have been used extensively. Plastic matrix tablets have delayed action because the dissolved drug has to diffuse through a capillary network between the compacted polymer particles. Commonly used plastic matrix beds are polyvinyl chloride, polyethylene, vinylacetate /vinyl chloride copolymer, vinylidine chloride /acrylonitryle copolymer, acrylate methacrylate copolymer, ethylcellulose, celluloseacetate, and polystyrene. Plastic matrix tablets in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure can be easily prepared by direct compression of drug with plastic material(s) provided that the plastic material can be comminuted or granulated to the desired particle size to facilitate mixing with drug particle or granulate for compression into tablets(10)

1.18 Embedding process:

Embedding process may be accomplished by:

1- Mixing and kneading of drug and plastic material with the solution of the same plastic material or other binding agent in an organic solvent and then granulated.

2- Dissolution of drug in organic solvent and granulated upon evaporation of solvent.

3- Using latex or pseudo-latex as granulating fluid to granulate the drug and the plastic mass.

Drug release from the inert plastic matrices is affected by varying formulation factors such as:

A- Matrix material

B- Amount of drug incorporated in the matrix.

C- Drug solubility in the dissolution media and in the matrix.

D- Matrix additives.

E- Release media.

Since the mechanism of controlling the drug release in the plastic matrix is the pre structure of the matrix, any formulation factors affecting the release of a drug from the matrix may be a consequence of their primary effect on apparent porosities and tortuosities of the matrices.

1.19 Release factors

Release factors can be summarized as follows:

A- The release rate increases as the solubility of the drug increases, but there seems to be no direct relationship between the two variables.

B- The release rate increases as the drug concentration increases. An increase in release rate cannot be explained on the basis of increasing matrix porosity. Rather it has been attributed to change in matrix tortuosity with drug concentration. And to decrease diffusion resistance by shortening the length of capillary joining any two drug particles.

C- It is possible to modify the release rate by inclusion of hydrophilic or hydrophobic additives to the matrix .The release of sparingly soluble substance can be increased by addition of physiologically inert but readily soluble material such as polyethylene glycol, sugars, electrolytes, and urea. The decrease in the release rate on the addition of hydrophobic substance may be due to decreased wettability of the matrix.

D- The release rate from plastic matrix tablets could be decreased by exposure to acetone vapor without changing the release mechanism. The extent of reduction is dependent on the amount of acetone absorbed.

E- The release rate increased as the particle size of the matrix material increased and as the particle size of the drug decreased.

F- Increasing compaction pressure up to the full consolidation point tends to decrease the pore formed among the polymer particles, resulting in slower drug-release.

The optimization of the efficacy of an active constituent often involves its availability at site of action. This gives the pharmaceutical companies a major concern to new drug delivery systems. In sustained release forms the release kinetics are not controlled but in controlled release forms the release kinetics can be adjusted by the design of the system, and can result in a constant plasma level within the therapeutic margin between the threshold of efficacy and toxicity (41).

1.20 Non-steroidal anti-inflammatory drugs (NSAIDS):

There are more than 50 different non –steroidal anti-inflammatory drugs (NSAIDS) on the market (42) as the NSAIDS include a variety of different chemical class. They have the major effects: Anti-inflammatory, analgesic and anti-pyretic effects.

All the three effects are mediated through the inhibition of cyclo-oxygenase and hence prostaglandins and thromboxanes .Cyclo-oxygenase (Cox) has two types Cox_1 & Cox_2. Cox_1 is a consecutive enzyme expressed in most tissues including blood platelets and tissue homeostasis. Cox2 is induced in the inflammatory cells and it is believed to be the enzyme that produces the prostanoid mediators of inflammation. Most NSAIDS inhibit both Cox_1 & Cox_2 (43).

Non–steroidal anti-inflammatory agents act by inhibition of prostaglandin at one or more points in the indo-peroxide biosynthetic ways and desensitize blood vessels to the permeability effects of other mediators of inflammation (44). This inhibition of prostaglandin leads to the anti-inflammatory effects of NSAIDS. The bad side effects of the abdominal irritation is due to the inhibition of the cyto-protective effect prostacyclin on gastric mucosa (45). NSAIDS are generally weak acids, highly protein bound, and those with a higher pka have a longer duration of action.

Numerous publications had been written about the release of non-steroid anti-inflammatory drugs to treat rheumatoid pains rheumatoid arthritis and osteoarthritis (45)

1.21 Diclofenac Sodium:

Diclofenac sodium is one of the most popular drugs which have superior use over other steroidal anti-inflammatory drugs. Diclofenac Sodium as a non-steroidal anti-inflammatory drug is used for relief of pain and inflammations in various conditions as:

A- Musculo-skeletal and joint disorders as rheumatic pain.

B- Peri-articular disorders such as persitis and tendonitis.

C- Soft tissue disorders such as sprains and strains.

D- In painful renal colic.

E- Acute gout.

F- Dysmenorrhea.

G- After surgical operations.

The adverse side effects include gastrointestinal disturbances, which may lead to peptic ulcer and severe gastro-intestinal bleeding. Epi-gastric pain, nausea, vomiting and diarrhea .Other side effects include hypersensitivity, tinnitus, depression, drowsiness and insomnia.

Diclofenac sodium is a Sodium salt of 2-[(2,6-dichlorophenyl) amino]phenyl] acetate. Diclofenac Sodium is practically insoluble in acidic solution (pka =4.0), but it dissolves at the intestine medium and water. Its Structural formula is $C_{14}H_{10}CL_2N\ NaO_2$.

1.21.1 Mechanism of action of Diclofenac sodium:

The mechanism of anti-inflammatory antipyretic analgesic action is through inhibition of prostaglandin synthesis by inhibition of cyclo-oxygenase (Cox). Diclofenac inhibit lipo-oxygenase pathway thus reducing the formation of leukotrienes. There is also speculations that Diclofenac may inhibits phospholipase A_2. Inhibition of Cox also decreases prostaglandins in the epithelium of the stomach making it more sensitive to corrosion by gastric acid.

1.21.2 Pharmacodynamics:

Diclofenac acts by the inhibition of prostaglandins biosynthesis which plays an important role in the causation of inflammation, pain, and fever. In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness and swelling of the joints.

1.21.3 Pharmacokinetics:

Judged by renal recovery of Diclofenac and its metabolites, the same amount of Diclofenac is released and absorbed from Diclofenac slow release and enteric coated tablets (46). Presumably due to a rate–dependent first pass effect, the systemic availability of Diclofenac from Diclofenac slow release is on the average of about 82 to 84% of the same dose administered as enteric-coated tablets. As a result of a slower release of the active substance from Diclofenac slow release, peak concentrations attained are lower than those achieved following the administration of enteric coated tablets. Mean peak concentration of 0.5 μg/ml or 0.4 μg/ml

(1.6 or 1.25 μmol/liters) are reached on the average about four hours after ingestion of a slow release tablet of 100 mg or 75 mg .On the other hand mean plasma concentrations of 13 ng/ml (40 nmol/litre) can be recorded at 24 hours after administration of Diclofenac slow release 100 mg (46). Food has no clinically relevant influence on the absorption and systemic availability of Diclofenac (Voltaren SR) (46).

Since about half the active substance is metabolized during its first passage through the liver (first pass effect). The area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size. Diclofenac is bound to serum protein at a rate of 99.7%, chiefly albumin 99.4% (46). The total systemic clearance of Diclofenac in plasma is 263 $\pm$ 56 ml/min (mean value $\pm$SD) The terminal half life is 1-2 hours after intravenous or oral administration of conventional dosage forms. Pharmacokinetic behavior remains unchanged following repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. Trough concentrations are around 22ng/ml or 25 ng/ml (70 nmol/litre or 80 nmol/litre) during treatment with Diclofenac slow release 100 mg once daily or 75 mg twice daily.

The bio-transformation of Diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylations followed by glucuronidation. About 60% of the administered dose is excreted in the urine in the form of metabolites as one of these two processes. Less than 1% is excreted as unchanged substance; the remainder of the dose is eliminated as metabolites through the bile in the faeces. No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed. In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics where

applying the usual dosage schedule. At a creatinine clearance of < 10ml/minute, the theoretical steady-state plasma levels of metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism of Diclofenac are the same as in patients without liver disease (46)

1.21.4 The indications of Diclofenac are:

A- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis; ankylosing spondylitis osteo-arthrosis and spondylarthritis.

B- Painful syndromes of the vertebral column.

C- Non-articular rheumatism.

D- Painful post-traumatic and post-operative inflammation and swelling.

E- Painful and/or inflammatory conditions in gynecology e.g. primary dysmenorrhea or adnexitis.

1.21.5 Contra-indications:

A- Hepatic ulcer

B- Hypersensitivity to the active substance.

C- Asthmatic patients, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or by other drugs with prostaglandin-synthetase inhibiting activity.

1.21.6 Adverse reactions

The adverse reactions include the following:

1- Gastro-intestinal tract

2- Central nervous system

3- Skin

4- Kidney

5- Liver

6- Blood

7- Hypersensitivity

8- Other organ systems

1.21.7 Action on gastro-intestinal tract:

Occasional: epi-gastric pain, other gastro-intestinal disorders such as nausea, vomiting, diarrhea, abdominal cramps, dyspepsia, flatulence, anorexia.

Rare: gastro-intestinal bleeding haemato-emesis, Melina, peptic ulcer with or without bleeding or perforation, bloody diarrhea (46).

In isolated cases: lower gut disorders such as non-specific hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's proctocolitis; aphthous stomatitis; glossitis; esophageal lesions; and constipation.

1.21.8 Action on central nervous system:

Occasional: headache, dizziness, vertigo and rare drowsiness. In isolated cases: disturbance of sensation, including paraethesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, taste alteration disorders .

1.21.9 Action on skin:

Occasional: rashes or skin eruptions. Rare urticaria.

In isolated cases: bullous eruptions, eczema, erythema multiform, Stevens-Johnson syndrome, Yell's syndrome

(Acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura, including allergic purpura.

1.21.10 Action on kidney:

In isolated cases: acute renal failure, urinary abnormalities such as haematuria, proteinuria (46). Interstitial nephritis, nephritic syndrome, and papillary necrosis.

1.21.11 Action on Liver:

Occasional: elevation of serum aminotransferase enzymes (SGOT, SGPT).

Rare: hepatitis with or without jaundice.

In isolated cases: fulminant hepatitis.

1.21.12 Action on Blood:

In isolated: thrombocytopenia, leucopenia, anemia

(Hemolytic anemia) agranulocytosis.

1.21.13 Hypersensitivity:

Rare: hypersensitivity reactions such as asthma, anaphylactic or anaphlactoid systemic reactions including hypotension. Other organ systems, rare oedema. In isolated cases impotence, palpitation, chest pain hypertension.

1.21.14 Precautions:

Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal dis-orders, with a history of suggestive gastro-intestinal ulceration, with ulcerative colitis or with Cronhn disease as well as in patients suffering from severe impairment of hepatic function.

Gastro-intestinal ulceration or bleeding of Diclofenac is more serious in elderly. They can occur any time during treatment with or without warning symptoms or a previous history. In this case of receiving Diclofenac the treatment should be stopped.

Owing to the importance of prostaglandins for maintaining renal blood flow particular caution should be made in patients with impaired cardiac or renal function, in the elderly, in patients being treated with

diuretics and in those with extra-cellular depletion e.g. in pre or post operative phases in major surgical operations . So monitoring of renal function is essential in Diclofenac usage. Diclofenac should be used with the lower effective dose in elderly and lower body weights.

As with other non-steroidal anti-inflammatory drugs elevation of one or more liver enzymes may occur with Diclofenac. During prolonged treatment with Diclofenac monitoring of hepatic function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, Diclofenac should be discontinued .During prolonged treatment with Diclofenac as with other anti-inflammatory agents blood counts are recommended (46).

1.21.15 Pregnancy and lactation:

During pregnancy Diclofenac should be employed only for compelling reasons and only in the lowest effective dose, particularly in the last 3 months of pregnancy owing to the

possibility of uterine inertia and /or premature closure of the ductus arteriosus. Following oral doses of 50 mg of Diclofenac administered every 8 hours, the active substance pass into the breast milk, but in small quantities with negligible effects on the infants.

1.21.16 Effect on ability to drive:

While taking Diclofenac patients experiencing dizziness or central nervous system disturbances should avoid driving vehicles (46)

1.21.17 Interactions:

When Diclofenac is given with digoxin plasma concentration was elevated. Various non-steroidal anti-inflammatory agents are liable to inhibit the activity of diuretics. Concomitant treatment with potassium sparing diuretic may be associated with increased serum potassium levels. Thus making it necessary to monitor the latter. Concomitant administration of systemic no steroidal anti-inflammatory agents may increase the occurrence of side effects.

Although clinical investigation does not appear to indicate that Diclofenac has an influence on the effect of anticoagulants. There are isolated reports of an increased risk of hemorrhage with the combined use of Diclofenac and anti-coagulant therapy. Therefore close monitoring of such patients is recommended. As with other non-steroidal anti-inflammatory agents, Diclofenac in a high dose can temporarily inhibit platelet aggregation.

Clinical studies have shown that Diclofenac can be given together with oral anti-diabetic agents without affecting their clinical effect (46).

Caution should be exercised when non-steroidal anti-inflammatory drugs are administered less than 24 hours before or after treatment with methotrexate , since the blood concentration of methotrexate may rise and toxicity of this substance may be increased. Increase nephrotoxicity of cyclosporine may occur through effects of non-steroidal anti-inflammatory drugs on renal prostaglandins (46).

1.21.18 Dosage and administration:

The administration of Diclofenac controlled slow release is according to the case of treatment. The dose is 100-150 mg administered as single or divided dose to be taken with liquid preferably at meal times.

1.21.19 Overdose:

Management of acute poisoning with non-steroidal anti-inflammatory agents consists of supportive and symptomatic measures. There is no clinical picture resulting of overdose of Diclofenac. In case of overdose treatment may be initiated by gastric lavage and activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression. Specific therapies such as forced dieresis, or dialysis is of no help in eliminating non-steroidal anti-rheumatic agents because of their high protein binding rate and extensive metabolism.

Rationale and Objectives

2.1 Rational and

Various matrices for controlled delivery systems were developed, from the simple matrix, coated pellets, microcapsules, ion exchange resins, hydrogels, to osmotic pumps (47)

This study is carried out to preparation of di ns of hydrophilic, hydrophobic, natural and semi-synthetic gums as controlled release matrices, and studied the in vitro release erent simulated physiological pHs similar to that of GIT pHs {1-8} (47). The in vitro drug patter e effectiveness of these combinations controlled systems by

A plot o on semi-log paper was made and the AUC$_{24}$ was calculated the trapezoid method.

matrix delivery systems with controlled action to overcome this problem.

AU

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For

for

$AUC_{0-\infty} = \sum AUC_{24} + \{C_{last} (reading_{24})\} / K_{el}$ (54).

Hydrophilic matrix hydroxypropylmethylcellulose (HPMC) (6), hydrophobic matrix acrylic ac and methacrylate derivatives (Eudragit L100)(48) natural gu d gum Arabic), combination of semi-synthetic and natu an gum plus gum Arabic) (49) all in different proportions were used as controlled release matrices.

In vitro release profiles were studied for the matrix controlled release Diclofenac sodium tablets (MT20, MT33, MT34) to see the similarity of these delivery systems compared to Voltaren retard (V.R) in gradient pHs (1.2, 2.1, 4.2, 5.5, release kinetics was also evaluated.

The study of controlled release Diclofenac sodium from different matrices has a scientific and economical value.

The rate of absorption was calculated from the following parameters C_{max}, T and MT33. The control (Diclofenac sodium from Novartis®) was compared with MT33.

The mean residence time MRT, the area under the moment concentration curve to infinity, and area under the curve to infinity were calculated.

The clearance of the drug from the body was also calculated from the dose over the area under the curve to infinity. (53) D/AUC$_\infty$

C_{max}, T_{max} were obtained from the data or the p ation versus time. The standard (Voltaren retard) was compared with the vitro drug patter sample MT33.

The fate of elimination was calculated from the plot of concentration a paper at terminal phase to obtain K_{el}.

$AUMC_{0-\infty} = AUMC_t + C_{last}/(K_{el})^2$

$T_{1/2}$ was calculated from Ln 2 e rate of elimination

$T_{1/2} = 0.693/K_{el}$ (mean) (56).

The mean residence time MRT was calculated from equation

$MRT = AUMC_{0-\infty}/AUC_{0-\infty}$.

Absorption rate = $C_{max}/AUC_{0-\infty}$

Eliminat ed from the

2.2 General objectives of study:

2.2.1- Manufacture a controlled release Diclofenac with similar attributes of the enteric controlled release brands.

The slope of θ

Slope = K_{el}

The elimination rate constant was determined as the slope of the linear regression of the Ln transformed plasma concentration versus time data in the terminal phase of the plasma concentration curve.

3.4.10 Statistical analysis:

Statistics using p-value was used to assess the differences between the pharmacokinetic parameters of controlled release matrix (MT33) compared to Diclofenac sodium from Novartis®. To evaluate the C_{max}, T_{max} AUC_{0-t}, $AUMC_{0-t}$, $AUC_{0-\infty}$, $AUMC_{0-\infty}$, K_{el}, $T_{1/2}$, C_{max}/AUC_{0-t} student-test was used to compare the two means at 95% confidence intervals of the data or the Ln value of the non uniform data using SPSS software ver 10.

3.4.11 validation of analytical method:

The analytical method of high performance liquid chromatography using the above specified portions of buffer, and C18 column was validated for precision (SD $\pm$ 0.42), accuracy (average recovery 100.36%), specificity (Percentage agreement 105.32%), linearity (within 0.2 $\mu g/ml^{-1}$ μg /ml) and limit of detection (LOD) was 10 ng /ml.

3.5 Quantitative analytical techniques:

3.5.1 Instrumentation:

Analysis of the matrices (MT20, MT33, and MT34) was performed using high performance liquid chromatography (HPLC) system consisting of Knauer K1001 isocratic pump and K-2501 ultra-violet visible spectrophotometer Knauer Germany at 254 nm. A rheodyne injection valve with 20 μl fixed filling loop. The analytical columns were C8, Eurosphere-100 (5 μm) 4.6 mm ID x 250mm with pre-column, and C18, Eurosphere-100 (5 μm) 4 mm ID x 100 mm. Both systems were

coupled with degasser Knauer and Eurochrome 2000 software for HPLC analysis.

3.5.2 HPLC Conditions:

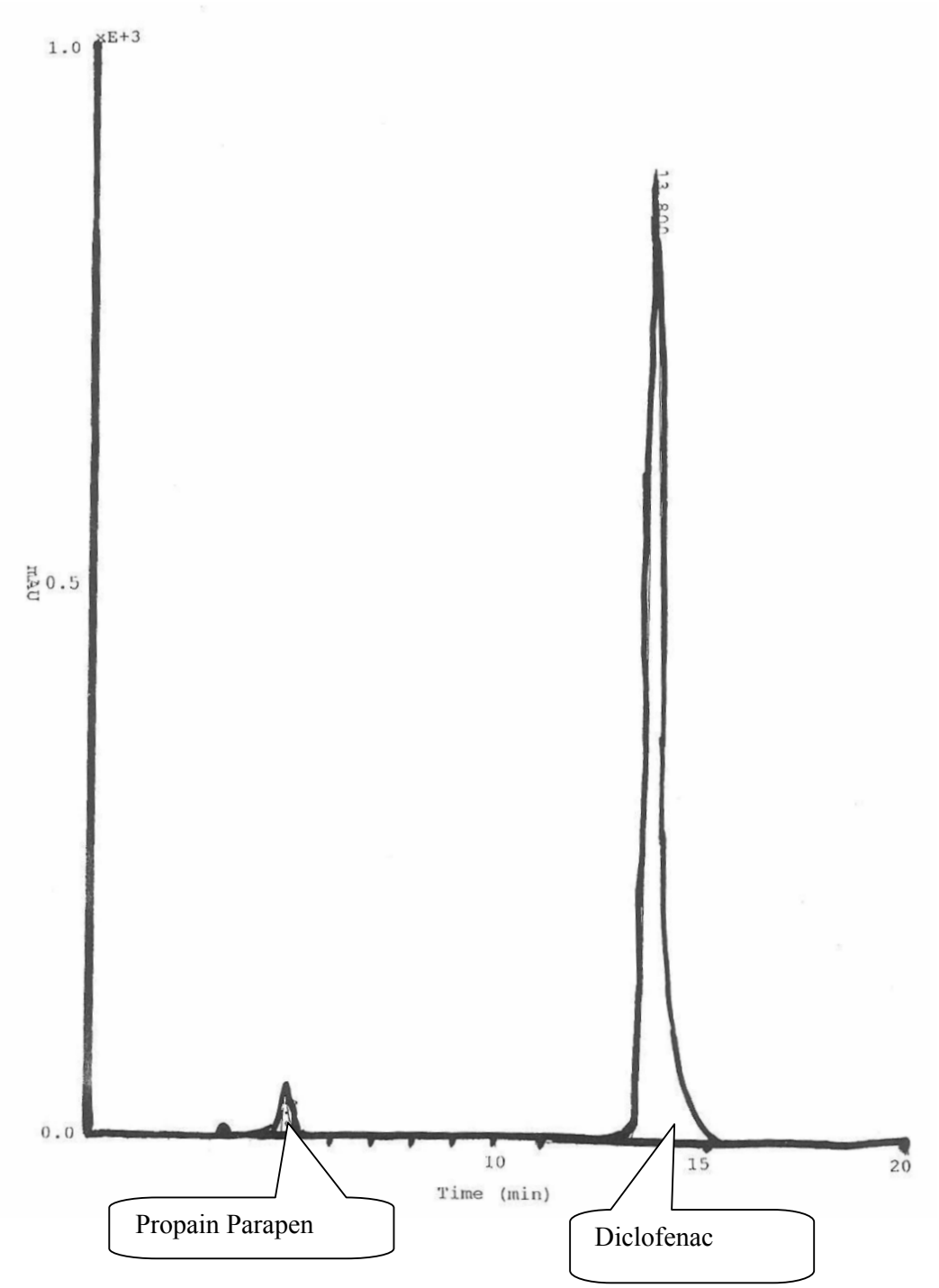
The mobile phase was degassed phosphate buffer ((0.1% W/V solution orthophosphoric acid and 0.16% sodium dihydrogenorthophosphate) adjusted at pH 3.5 (34 volumes) plus (66 volumes) methanol (57).

3.5.3 Sample preparation and standards:

The stock solution of the three matrices (MT20, MT33, MT34) were prepared by crushing of 10 tablets of each sample and the average amount of 100 mg was taken to it 0.1% orthophosphoric acid and 0.16% sodium dihydrogenorthophosphate)/methanol (34:66 V/V) solution (mobile phase), was added in a 100 ml measuring flask. The internal standard, Ibuprofen, was added (1 mg/ml). The mixture was stirred for about 15 minutes, filtered through Whatman No1 filter paper and adjusted to volume. The standard Diclofenac sodium was treated in the same manner. All standard and samples were 1mg/ml concentration. Giving the same overlapped peaks, Ibuprofen was replaced by propylparaben as internal standard.

3.5.4 Assay: Sample analysis:

20 µl of each sample and standard were injected each time.



Chromatogram of Diclofenac from plasma with internal standard

3.6 In vitro/in vivo correlation:

In vitro in vivo correlation (IVIVC) has been defined by US pharmacopoeia (USP) as the establishment of a relationship between a biological property, or a parameter derived from a biological property produced by a dosage form and a physicochemical characteristic of the same dosage form. FDA defined IVIVC as a predictable mathematical model describing the relationship between an in vitro property (usually the extent or rate of release) and a relevant in vivo response (e.g. plasma concentration or amount of drug absorbed). In vitro in vivo (IVIVC) is guidance for product development.

3.6.1 Categories of correlation:

The IVIVC was categorized by FDA into 3 levels, level A, B, and C (2)

Level A:

Is a predictive mathematical model for relationship between the entire in vitro release time and entire in vivo response time e.g. for plasma drug concentration or amount of drug absorbed.

Level B:

A predictive mathematical model for relationship between summary parameters that characterize the in vitro and in vivo time coarse e.g. relate mean in vitro dissolution time to the mean in vivo dissolution time or the mean residence time in vivo.

Level C:

A predictive mathematical model for relationship between the amount dissolved in vitro at a particular time e.g. (Q60) or the time required for dissolution of a fixed amount ($T_{50\%}$) and the in vivo parameters C_{max}, AUC_{0-t} (2)

Using level A, in vitro in vivo correlation was done for both Voltaren retard and MT33.

The in vitro dissolution curve was compared to the drug plasma release curve which was obtained from the simple superimposition of the two mentioned curves which indicate the correlation. A plot of the fraction absorbed in vivo versus the fraction released in vitro was made. This relation is often linear with slope greater than 0.95. The intercept may or may not be zero, depending on the lag time for in vivo release or the non-instantaneous absorption rate resulting of dissolved non-absorbed drug.

Currently accepted criteria are 80-125% of the reference using 90% confidence interval.

Table (3.5): Voltaren retard in vitro in vivo correlation data.

Time hr.	Plasma C. µg/ml.	Amount dissolved mg/ml	Ln Value of amount dissolved
0.5	0.2047	0	-2.01216
1	0.2167	0.1337	-1.38669
2	0.233	0.2499	-1.06711
3	0.2406	0.344	-0.8308
4	0.2482	0.4357	-0.68856
5	0.2481	0.5023	-0.46061
6	0.2479	0.6309	-0.38802
7	0.2607	0.6784	-0.318
8	0.2735	0.7276	-
10	0.3063	-	-
12	0.2907	-	-
24	0.3087	-	-

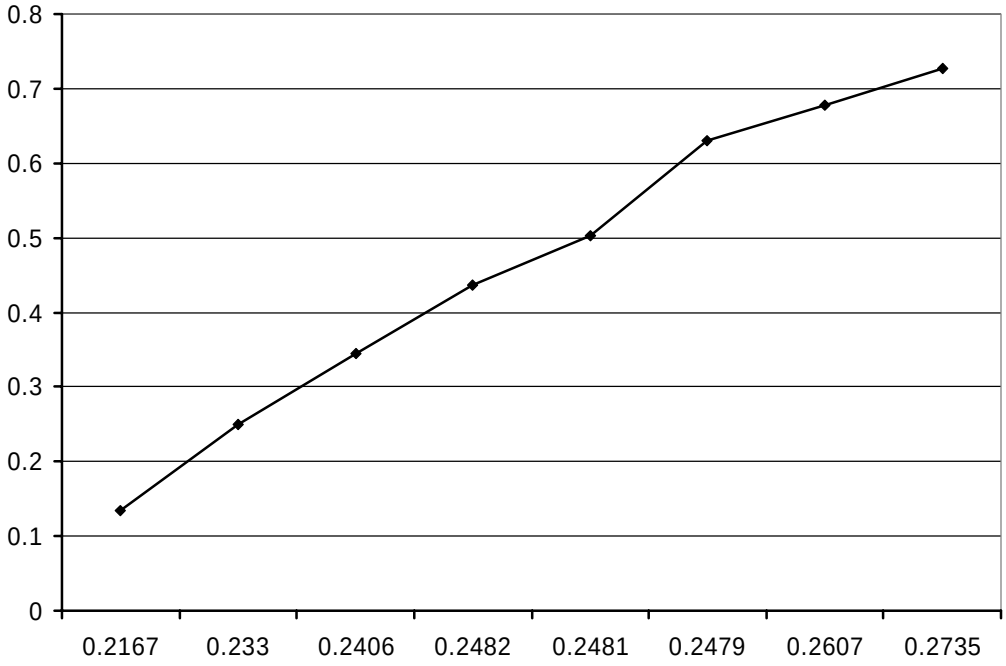


Figure 3.3 In vitro in vivo correlation of Voltaren retard.

Table (3.6): MT33 in vitro in vivo correlation data

Time Hr.	Plasma C. µg/ml.	Amount dissolved mg/ml	Ln Value for amount dissolved
0.5	0.2595	0	-2.67365
1	0.2706	0.069	-1.90381
2	0.2967	0.149	-1.35518
3	0.3034	0.2579	-0.9835
4	0.3101	0.374	-0.74866
5	0.3001	0.473	-0.57803
6	0.2901	0.561	-0.4684
7	0.3055	0.626	-0.37251
8	0.3209	0.689	-
9	0.3176	-	-
10	0.3142	-	-
11	0.3238	-	-
12	0.3333	-	-
24	0.4112	-	-

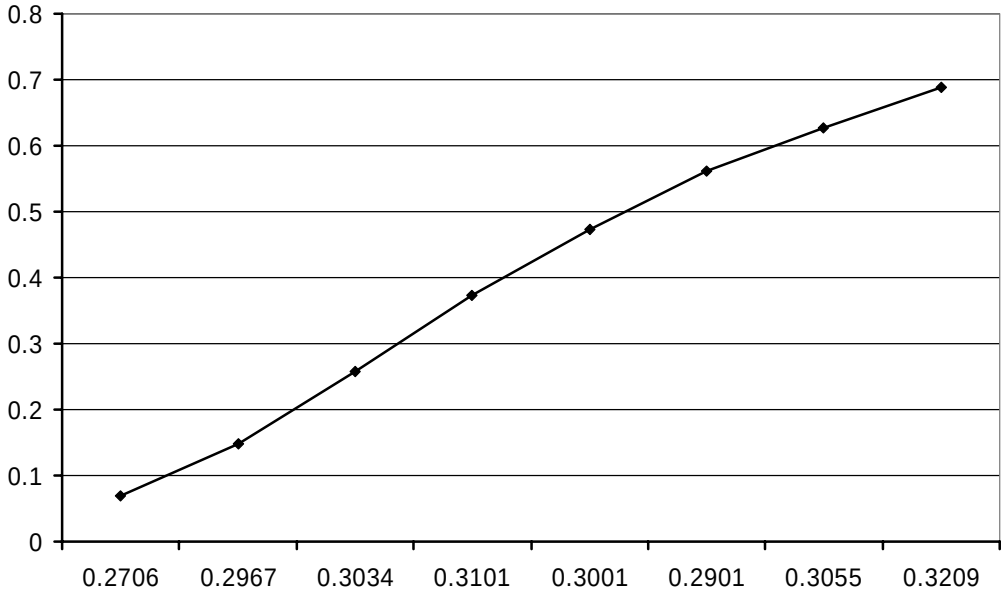


Figure (3.4): In vitro in vivo correlation of MT33

Table (3.7): Ln values of diclofenac sodium from Voltaren retard (in vitro dissolution and in vivo plasma concentration).

Ln values of in vitro Diclofenac concentrations	Ln values of in vivo Dicloenac concentrations
2.01216	1.58621
1.38669	1.529241
1.06711	1.456717
0.8308	1.424619
0.68856	1.39352
0.46061	1.393923
0.38802	1.39473
0.318	1.344385

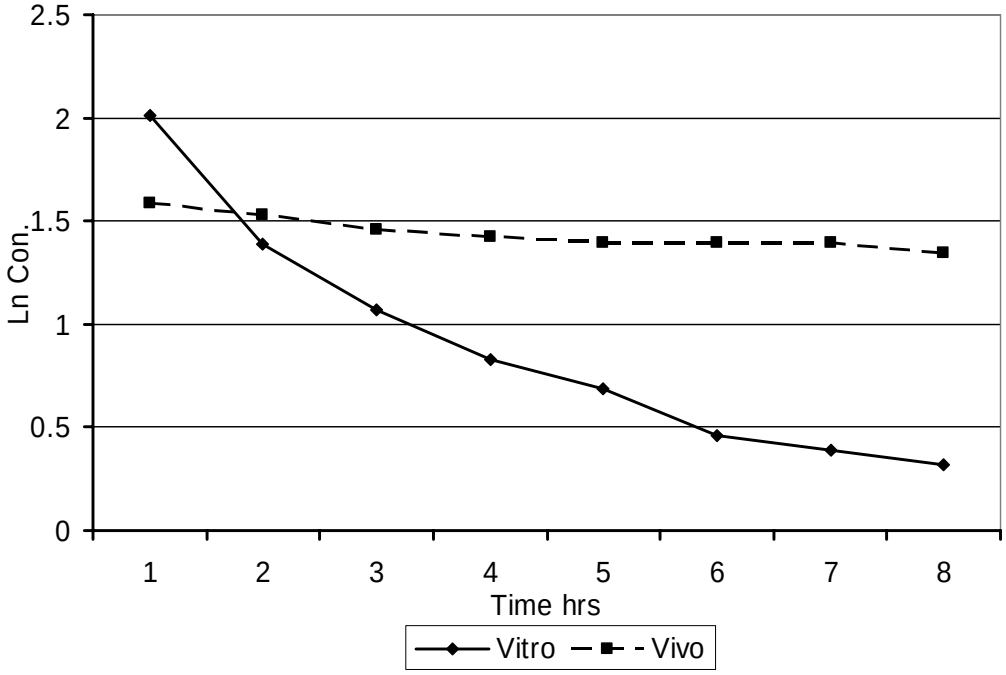


Figure (3.5): Correlation of Ln values of Diclofenac sodium released from Voltaren retard (in vitro dissolution and in vivo plasma concentration).

Table (3.8): Ln values of Diclofenac sodium concentration from MT33 (in vitro dissolution and in vivo plasma concentration).

Ln values of in vitro Diclofenac concentrations	Ln values of in vivo Diclofenac concentrations
0.2047	1.349
0.2167	1.3071
0.233	1.215
0.2406	1.1927
0.2482	1.1708
0.2481	1.2036
0.2479	1.2375
0.2607	1.1858

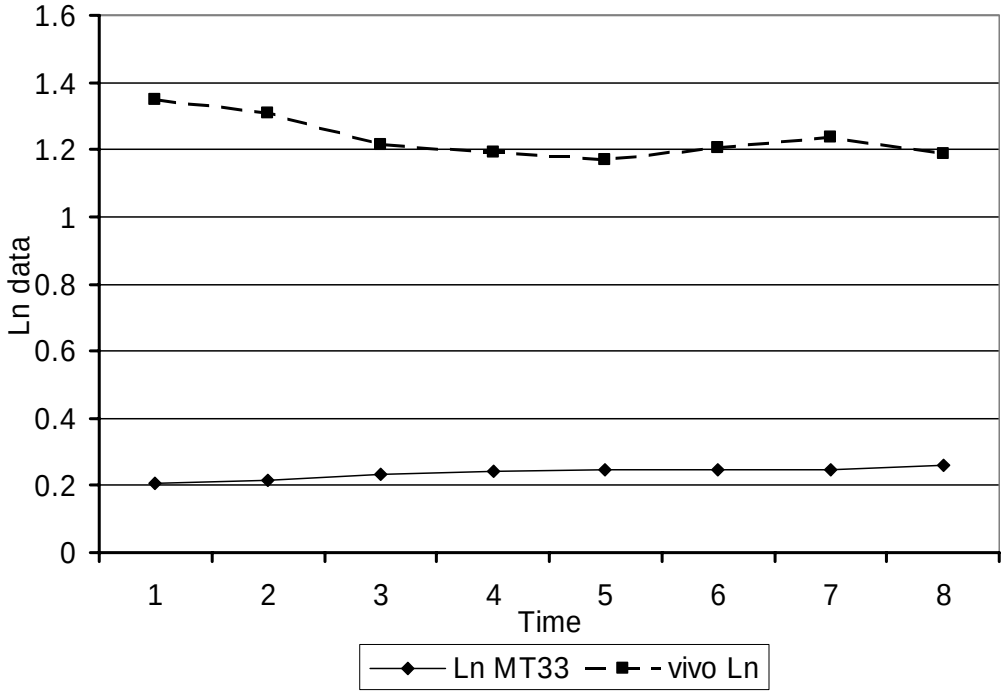


Figure (3.6): Correlation of Ln values of Diclofenac sodium released from MT33 (in vitro dissolution and in vivo plasma concentration).

3.7 Accelerated stability study of matrix tablets:

The USP/NF has required expiration dates for all monograph drugs since January 1976 (10). The label should bear the expiration date limiting the period during which the oral tablet retains its full label potency if stored as directed. A set of storage temperatures was provided by USP/NF to cover the various conditions of storage. From the freezing of -10 ^{o}C, refrigerator between 2 - 8 ^{o}C, cool place between 8-15 ^{o}C, control temperature between 15 -30 ^{o}C, room temperature, up to 40 ^{o}C with protection of light and moisture.

Accelerated stability based on chemical kinetics was demonstrated by Garret and carper since 1955 (58). The WHO stated that the temperature and relative humidity for the accelerated stability conditions in climatic zone 1V as 40 $\pm$ 2C^{o} /75% $\pm$ 5 RH for six months (59).

In 1971 the food and drug administration (FDA) published a set of guide lines, Manufacturing and controls for investigational new drug application (IND) and new drug application (NDA) which defined in greater details the stability information required for new drug application (10). The tablet physical parameters in IND phase 111 are surface appearance, friability, fragility, hardness, disintegration, color, weight variation, odor, and moisture and dissolution rate. Nowadays many guidelines were used for stability. They include ICH (International conference for Harmonization), CPMP (Committee for proprietary medicinal products) FDA (Food and drug Administration) and WHO (World Health Organization) (59-63).

The purposes of stability study are to ensure the efficacy, safety and quality of drug, and shelf life determination. In 1987 the FDA published the guidelines for submitting documentation for stability of human drugs and biologics (10). They include tests for appearance, friability, hardness, color, odor, moisture, strength, and dissolution. The

stability should include at least three batches in a marketing container used for study under the specified storage conditions. The factors affecting stability are storage time, storage conditions, type of dosage form and container and closure systems.

Stress conditions in accelerated stability studies (64) in multi-temperatures and Arrhenius equation were used for estimation of shelf life of drugs. The Arrhenius Approach has several drawbacks, which apply for drugs with determined rate of reaction and the linear regression is applied even though the data are not linear. Above critical temperature with change of degradation mechanism this approach is invalid (65)

In the Sudan, which has, different climatic conditions from the Sahara to the sub-tropical conditions made the stability of pharmaceuticals to be of crucial importance especially for a new drug delivery system.

The objectives of this study were to evaluate the content in accelerated stability of new matrix formulations of Diclofenac sodium 100mg which was proved to be controlled release matrix delivery system. We also assessed the microbiological burden in gum matrix tablets, comparing preserved tablets with non-preserved ones.

In a previous study (66) three controlled release matrix tablets from EudragitL100 6% plus Hydroxy-propyl-methyl-cellulose HPMC 20% (MT20). Guar gum15 % plus Gum Arabic 15% (MT33). Xanthan gum 15% plus Gum Arabic 5% (MT34) were proved to be as new oral drug delivery systems. The formulas, MT33, MT34 were preserved with both 0.18 % methylparaben and 0.02% propylparaben to give MT33p and MT34p consecutively.

The incorporation of gums especially acacia was reported to be susceptible to microbiological contamination (67). Being susceptible to

such deterioration it was necessary to preserve these (MT33, MT34) gum containing formulae. The compendia method (BP) stated a limited bio-burden in oral tablets with absence of the pathogenic bacteria as *E. coli*, *Salmonella typhi*, and Staphylococcus aurous.

Since a high temperature was considered in stability study 40 ^{o}C. The reaction rate of molecules is proportional to the collisions per unit time. Since the numbers of collisions increase with time the exponential dependence was as in Arhenius equation:

Log K = LogA - ΔH/2.303RT

K=Specific rate of degradation

R= gas constant (1.987 cal deg^{-1} mol^{-1})

A=Frequency factor (constant)

T=Absolute temperature (t ^{o}C+ 273.16 ^{o}C)

H=activation energy of the chemical reaction.

In the usual range of activation energy for tablets formulation decomposition is 10-20 mol^{-1} (10).

3.7.1 Materials and methods:

3.7.1.1 Chemicals and reagents:

All solvents were HPLC grade, while the other chemicals were of analytical grade. The standard Diclofenac sodium was from Horst von Valtier Hamburg, Germany. All solvents and reagents were purchased by Wafrapharma Laboratories Sudan. The internal standard was propylparaben from G. Amphray Laboratories India. Nutrient agar, Saubourauds dextrose agar was from Oxoid® LTD, Basingstroke, Hampshire, England.

The stability studies were conducted on the five matrix tablets (MT20, MT33, MT34, MT33p, MT34p) with reference to physical appearance and content after storage in stability chamber Rumed, Rubarth

Apparate GmbH Germany, at 45 ^{o}C and 75% relative humidity for 6 month (WHO reg.).

3.7.1.2 Instrumentation:

The stability studies were conducted on the five matrix tablets (MT20, MT33, MT34, MT33p, and MT34p) prepared by direct compression method containing 100 mg Diclofenac sodium. They all proved to be potentially controlled release matrix delivery systems.

The study was done in darkened chamber (68). The storage conditions were used for zone 1, 11,111, and 1V for accelerated stability study (40 ^{o}C and 75%RH) which was designed for solid oral dosage forms, solids for reconstitution, dry and lyophilized powders in glass vials. Samples were kept in blister packing –PVC 250 µm, Aluminum foil 25 µm. Content analysis was performed using isocratic high performance liquid chromatographic method, using C18 column and mobile phase of phosphate buffer at pH 3.5 and acetonitrile in combinations of (65 and 35V/V). 20µL were injected each time, and flow rate was one ml/minute. Microbiological tests for matrix tablets(MT20, MT33, MT34, MT33p, MT34p) during accelerated stability study, were performed using BP 1999 method appendix XV1C (69).

3.8 Microbiological study during stability:

Microbiological tests were done for six consecutive months. 10 tablets from the controlled release matrix tablets were ground by triturating in a mortar. 100 mg 0f the resulting powder was dissolved in sterile 9ml sodium peptone buffer solution at pH 7. One ml from this solution was taken and transferred to a sterile test tube containing 9ml of sterile purified water. 9 ml sterile purified water was taken as a negative control.

1 ml from each of these tubes was transferred to a sterile Petri-dish, then the sterile nutrient agar or sterile Saubourauds dextrose agar was

poured in the Petri-dishes. Each experiment was done in replicates to minimize error. The nutrient agar plates were incubated at 32 ^{o}C for 48 hours to enumerate bacterial growth. Saubouraud dextrose agar was incubated at 25 ^{o}C for 72 hours to observe the fungal colonies (69)

Chapter IV

4. Results and Discussion

4.1 In vitro diffusion analysis:

The release from the different matrices MT20, MT33, MT34 and V.R in acidic pH 1.2 was less than 10% complying with the enteric – coated articles - general drug release standard (1). All these matrices are pH sensitive since the percentage release pattern was affected by pH change. At pH 2.1 MT20 and MT33 gave zero-order release with correlation coefficient(r) of 0.9977 and 0.9910, respectively.

At pH 4.2 the release profile of MT34 was parallel to V.R. The release was steady at pH 5.5 for all matrices. At pH7.2 all the four matrices MT20, MT33, MT34 and V.R gave zero order release with correlations (r) MT20, r = 0.9966, MT 33, r =0.9899, MT34, r = 0.9992 V.R, r = 0.9925 almost approaching unity (fig 4.7)

The drug release data were fitted to the following equation (70)

$Mt/M\infty = Kt^n$

Where $Mt/M\infty$ is the fraction of the released drug at time t, K is a constant related to structure and geometric characteristics of the release device (50). The diffusion exponents were 0.96, 1.15, 1.02 and 1.12 for MT20, MT33, and MT34, and V.R consecutively, showed case II type of release (zero order).

4.2 In vitro result and discussion

Figures 4.1, 4.2, 4.3, 4.4, 4.5, 4.6 and 4.7 showed in vitro release profiles for different matrices MT20, MT33, MT34 and V.R in different pH gradients.

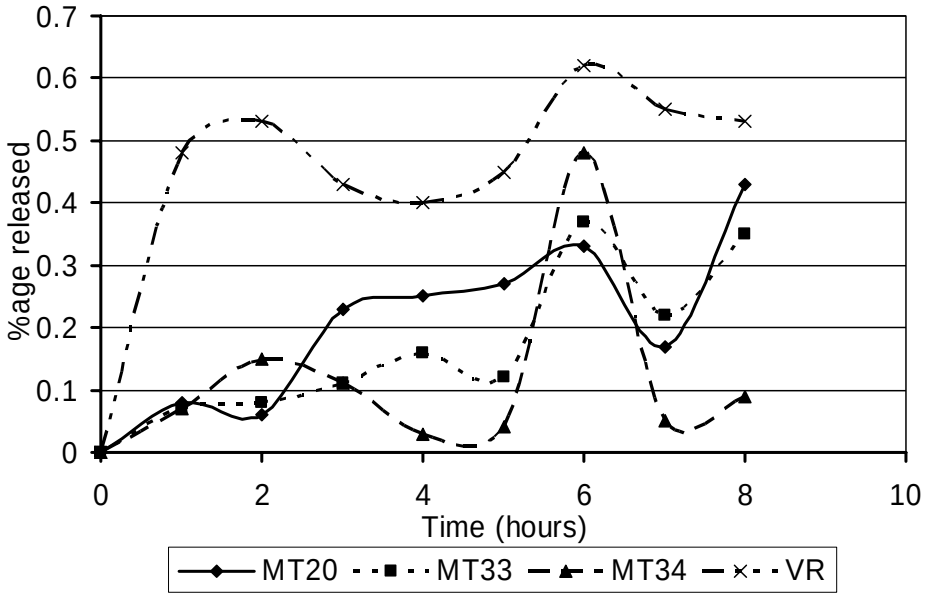


Figure (4.1): Percentage release of Diclofenac sodium at pH 1.2

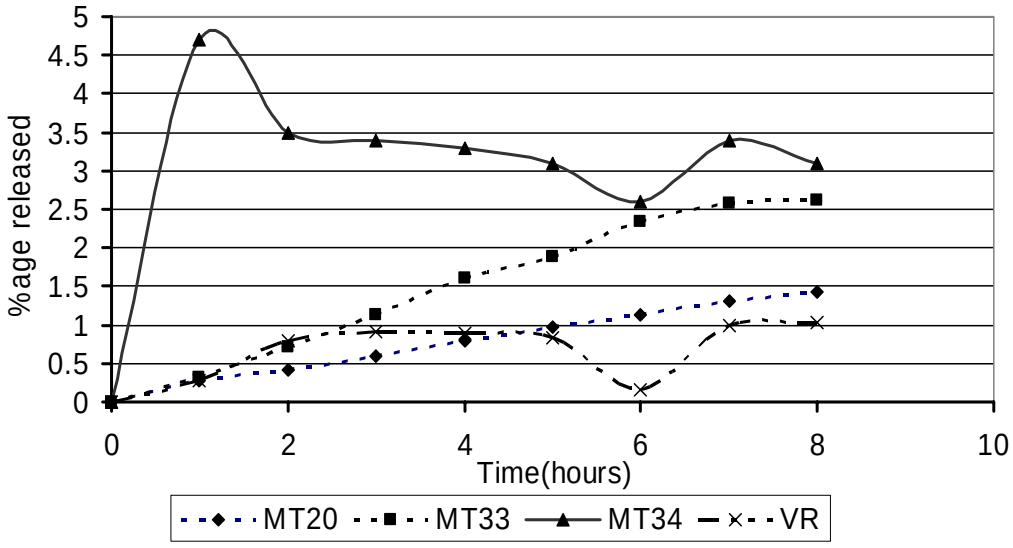


Figure (4.2): Percentage release of Diclofenac sodium at pH 2.1

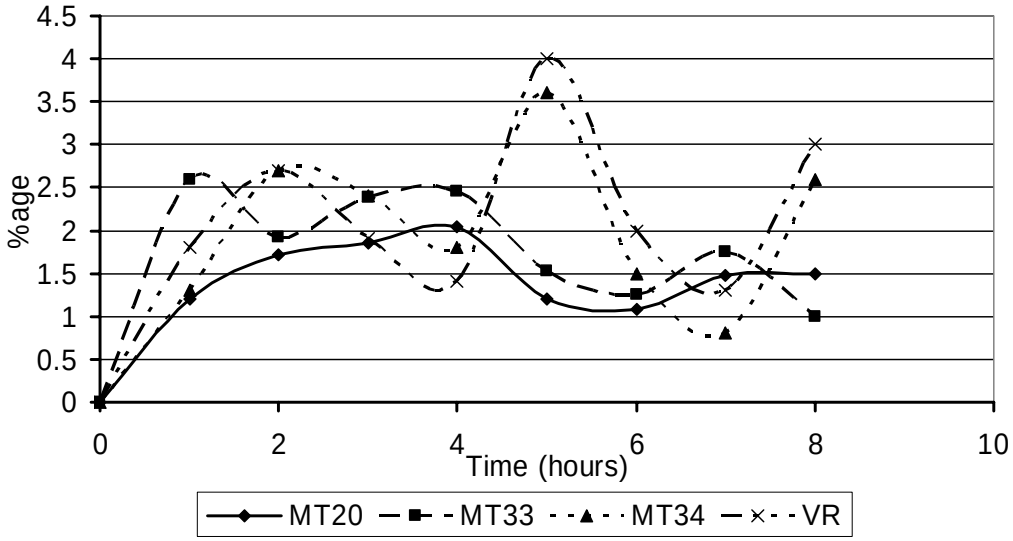


Figure (4.3): Percentage release of Diclofenac sodium at pH 4.2

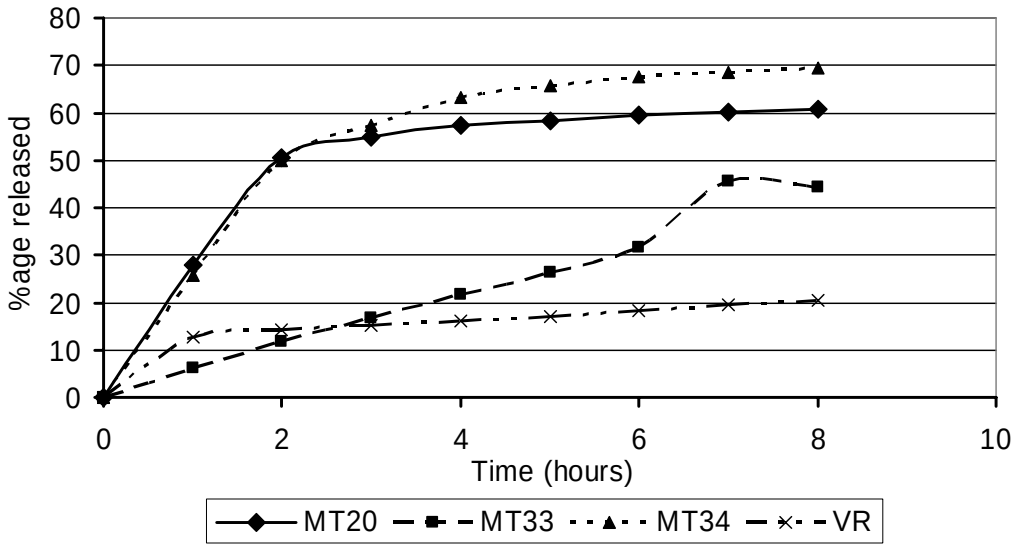


Figure (4.4): Percentage release of Diclofenac sodium at pH 5.5

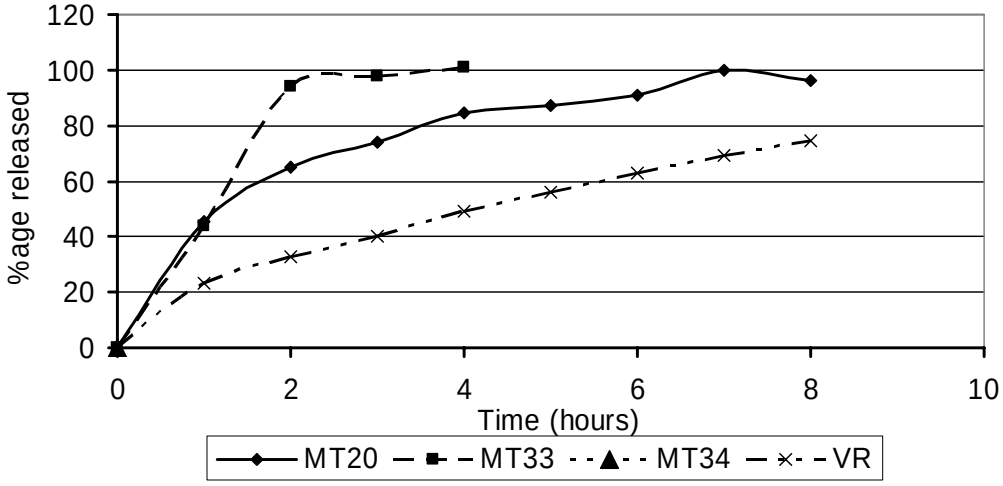


Figure (4.5): Percentage release of Diclofenac sodium at pH 6.5

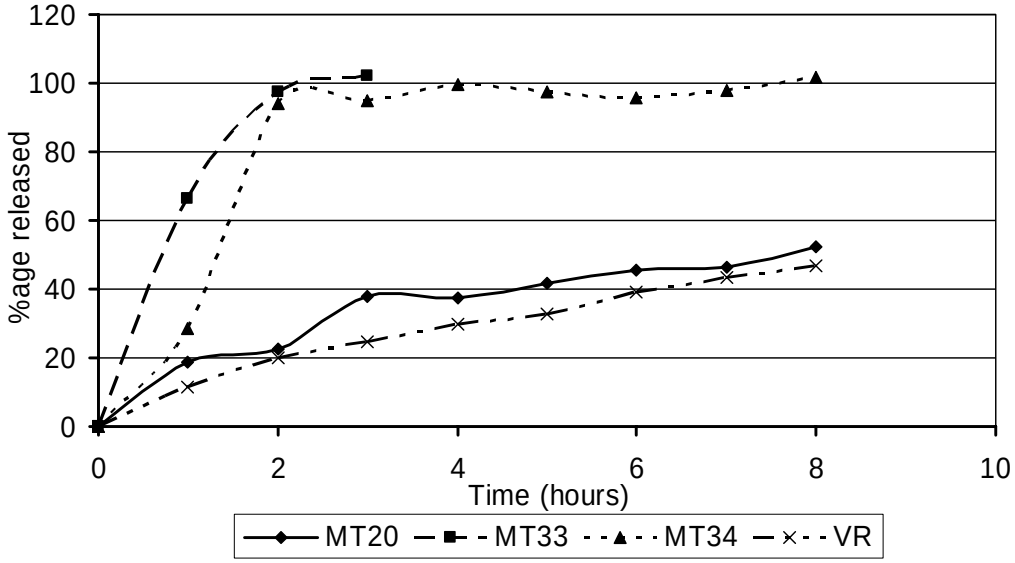


Figure (4.6): Percentage release of Diclofenac sodium at pH 6.7

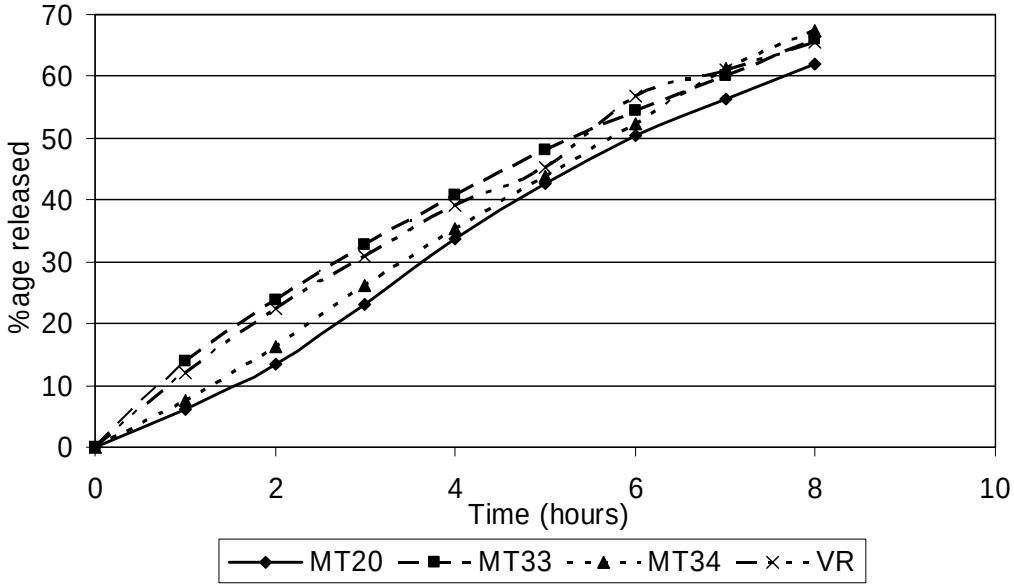


Figure (4.7): Percentage release of Diclofenac sodium at pH 7.2

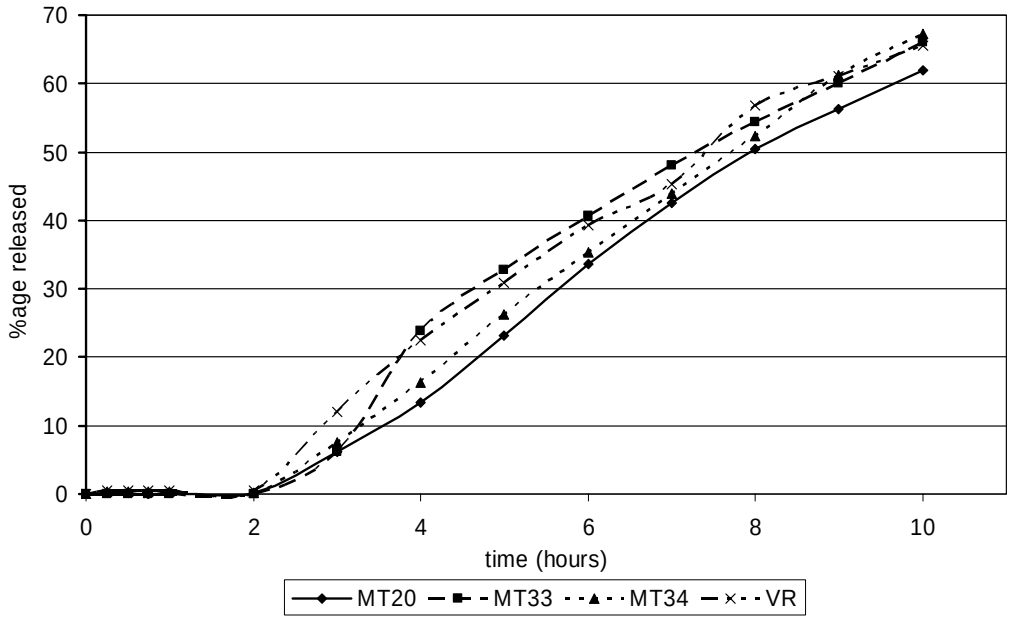


Figure (4.8): Percentage release of Diclofenac Sodium from acidic pH 1.2 and pH 7.2 buffer media

Table (4.1): Correlation coefficients comparison for different matrices and Voltaren retard

Model	Standards	Std. error	Pearson Correlation	Sig.**
1	VR	1.539	-	0.934
2	MT20	0.475	0.993	0.865
3	MT33	0.194	0.998	0.014
4	MT34	0.495	0.994	0.698

The change of pH changed the pattern of release according to figures 4.1 to 4.7. Within the matrix tablet the environment is almost neutral (Dibasic calcium hydrogen phosphate dihydrate) when the solvent entered the matrix the environment of the matrix was changed and the rate of release was changed which agreed with Al-Tanni, and Tashtoush (71) findings.

The above matrix tablets (MT20, MT33, MT34) showed drug release of about 60% after eight hours time in pH 1.2 and pH 7.2 consecutively (fig.4.8). HPMC as a non – pH dependent matrix (52) with combination of Eudragit L100 (anionic polymer based on methacrylic acid and methacrylate, with 50% free carboxylic acid group) in a ratio of 20% HPMC to 6% Eudragit L100 changed the matrix to a pH sensitive one, with release profile changed with pH change.

It has been reported that HPMC (72) and Eudragit L100 (71) separately gave controlled release matrix tablets and in combination of HPMC and Eudragit L100-55 also gave controlled release of Diclofenac (71). Eudragit L100 is similar to EudragitL100-55 but with less viscosity (73), despite of that it gave a controlled release matrix eroded at pH 5.5 and pH 7.2. Gum Arabic as a polysaccharide with heteropolysaccharide (Xanthan gum) formed a controlled matrix similar to guar gum plus gum Arabic but highly pH sensitive. Guar gum a galactomannan with Xanthan gum (heteropolysacharide) made cross-linking to form a controlled matrix agreed with Bhagwat *et al.* patency (USA patents 6,537,578), (49) but acacia alone has no controlled release action (74).

4.3 Analytical result and discussion

Sharp chromatograms were obtained each time for both C8 and C18 columns. The sample concentrations and the retention times using C8 column were shown in table 4.2. The retention time was found to be at about 14 minutes for C8. It was reported to be at 25 minutes for

Diclofenac sodium and 12 minutes for Diclofenac impurity at the detection wavelength 254 nm but at different analytical conditions (57).

When Diclofenac sodium was injected alone the Rt was 7.9 minutes. Ibuprofen when injected with Diclofenac sodium as internal standard, using C8 column the same retention time of about 13.3 minutes was obtained. The total peak areas (mAU*min) of both Diclofenac sodium and Ibuprofen (490.09) was almost equal to the summation of each separate peak area of Diclofenac sodium (438.11) and Ibuprofen(28.37), which was 466.478 with slight delay in retention time 13.7 minutes. This pathochromic shifts may be due to the interaction of the pair of electrons in Diclofenac sodium with Ibuprofen. Giving the same overlapped peaks, Ibuprofen was replaced by propyl-paraben as internal standard.

Analyzing the three matrix tablets using C18 column instead of C8, the retention time of Diclofenac sodium and peak area obtained were shown in table 4.3.

Table (4.2): Column C8 analysis: Content and Rt time:

Matrix	C.%	Rt in minutes	mAU*min
MT20	104	14.3	428.129
	101	13.6	424.415
	098	13.7	405.609
	099	13.0	435.174
	100	14.0	428.532
MT33	103	13.9	442.532
	100	13.7	418.828
	099	13.7	408.844
	096	12.9	421.488
	103	13.9	442.532
MT34	100	13.9	470.526
	101	13.7	425.847
	097	14.0	383.963
	100	13.2	436.544
	100	13.9	470.527
Standard Diclofenac	100	13.8	427.686

The retention time for Diclofenac from different matrices using C 18 was found to be about 8 minutes which was less than C8 (14 minutes).

Ibuprofen retention time was 7.9 minutes, and the peak areas of the sample and Ibuprofen was 402 mAU almost approaching 410 mAU of both analyte and internal standard.

Table (4.3): Column C18 analysis: Content and retention time (Rt)

Matrix	C%	Rt in minutes	mAU*min
MT20	106	7.5	416.836
	108	7.9	426.651
	107	7.9	424.015
	105	7.9	415.834
	106	7.9	420.051
MT33	104	7.5	410.970
	104	9.0	411.854
	107	8.0	422.784
	108	8.0	425.022
	106	8.0	417.083
MT34	096	8.9	466.779
	096	8.8	468.300
	096	8.0	467.634
	094	7.8	458.841
	099	7.8	483.879
Standard Diclofenac	100	8.0	486.737

Table (4.4): Statistics of content of tablets matrices (MT20, MT33, and MT34) using C8 and C18 columns

percentage content	N	Mean	Std. Deviation	Std. Error Mean	p-value
C8	15	100.0000	2.07	.53	0.062
C18	15	102.8000	5.06	1.31	

The C8 column (25cm) was longer than C18, (10 cm), while both columns were lined with the micro sphere –100. The long side butyl chain of Ibuprofen may delay the separation process making the Ibuprofen to be separated at a lower rate than the Diclofenac sodium big molecule. The time for analysis with C18 (8 minutes) was nearly half the time withC8 (13.7 minutes).

4.4 Bio-equivalence result and discussion

In bio-equivalence study of the previous matrices evaluated Cmax, Tmax, t1/2, rate of absorption, mean residence time and elimination rate constant of the investigated drug compared with control drug. The mean plasma concentration of both control (Voltaren retard) (VR) and MT33 were shown on table 4.5. The mean plasma profile was presented in fig 4.9.

Table (4.5): Mean and standard deviation of plasma concentration of both control (Voltaren retard,VR) and MT33

Time (Hours)	Voltaren retard	MT33
0.5	0.2047	0.2595
1	0.2167	0.2706
2	0.233	0.2967
4	0.2482	0.3101
6	0.2479	0.2901
8	0.2735	0.3209
10	0.3063	0.3142
12	0.2907	0.3333
24	0.3087	0.4112
Mean	0.2589	0.3118
SD	0.0380	0.0441
Minim.	0.2047	0.2595
Maxim.	0.363	0.4112
CV%	14.6775	14.1437

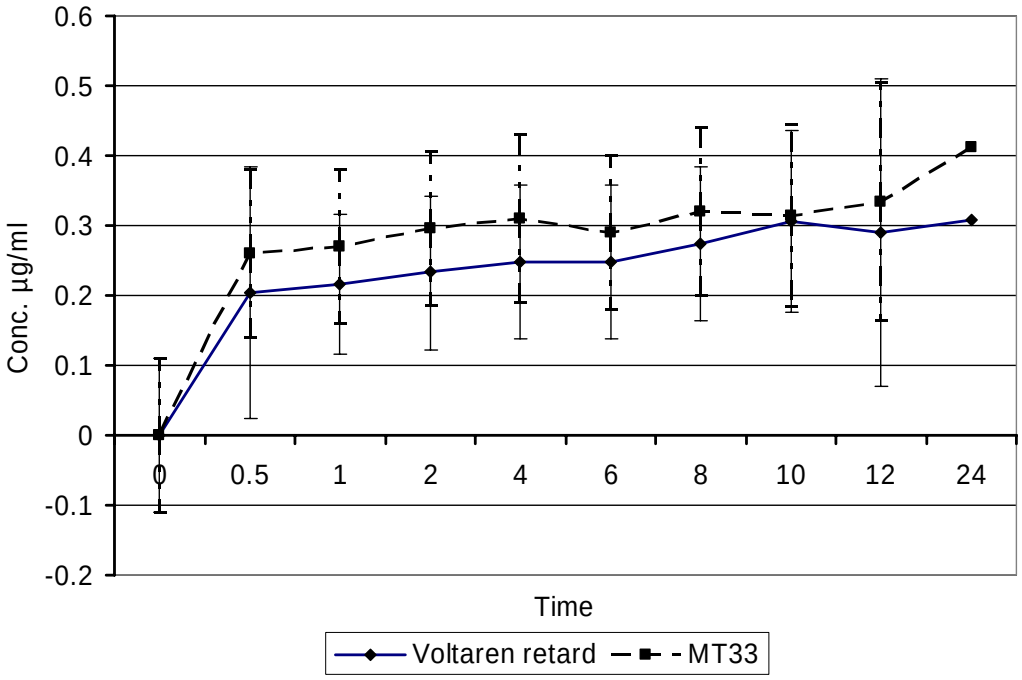


Figure (4.9): Mean (± SD) plasma concentration versus time profiles

Analysis of variance (ANOVA) was shown for plasma concentrations (F-value) for both control and MT33
(Table 4.6). No differences between control and MT33 at all levels of time up to 24 hours which advocate the bio – equivalence of the two products (53).

Table (4.6): Analysis of variance for bio-equivalence parameters

Parameter	Formulation	N	Mean ± SD	p-value
AUC0-24	VR MT33	12 12	7.059±0.36 7.776±0.36	0.401
AUC0-∞	VR MT33	12 12	32.693±1.18 35.052±1.18	0.799
Cmax	VR MT33	12 12	0.391±0.02 0.425±0.02	0.443
Tmax	VR MT33	12 12	12.333±0.13 12.583±0.13	0.936
Kel	 VR MT33	12 12	0.021±0.001 0.022±0.001	0.894
AUC0-24/AUC0-inf.	VR MT33	12 12	0.300±0.002 0.304±0.002	0.959
T1/2	VR MT33	12 12	41.375±0.79 39.795±0.79	0.936

The other data of all the bio - equivalent studies were shown in the following (tables 4.7 -4.29).

Table (4.7): Demographic Data and Sequence of administration of MT33 and Voltaren retard (100mg) to twelve healthy male volunteers

Subject No	Subject ID	Age Yrs	Height Cm	Weight Kg	Period 1	Period 2
1	MAH	26	180	76	A	B
2	KHN	25	164	60	A	B
3	MOH	28	162	50	A	B
4	ABA	31	173	53	A	B
5	ABH	35	163	70	A	B
6	MOA	25	167	58	A	B
7	MOR	24	169	55	B	A
8	MMO	25	172	58	B	A
9	SAM	41	171	76	B	A
10	YOA	44	179	86	B	A
11	MOM	25	173	65	B	A
12	ALA	23	170	55	B	A
Mean	-	29.33	170.25	63.50	-	-
$\pm$SD	-	7.02	5.74	11.17	-	-

Table (4.8): Plasma concentrations (µg/ml) of Voltaren retard (100mg) after oral administration to twelve healthy male volunteers

No	Subject	time	0.5	1	2	4	6	8	10	12	24
1	MAH	0	0.299	0.326	0.323	0.373	0.400	0.371	0.385	0.458	0.253
2	KHN	0	0.281	0.282	0.355	0.357	0.385	0.438	0.493	0.625	0.215
3	MOH	0	0.316	0.326	0.133	0.115	0.345	0.352	0.400	0.510	0.224
4	ABA	0	0.207	0.217	0.230	0.258	0.286	0.415	0.302	0.319	0.126
5	ABH	0	0.378	0.341	0.359	0.416	0.250	0.310	0.311	0.401	0.382
6	MOA	0	0.172	0.208	0.168	0.173	0.199	0.227	0.231	0.197	0.143
7	MOR	0	0.169	0.224	0.222	0.225	0.377	0.374	0.198	0.162	0.165
8	MMO	0	0.227	0.220	0.155	0.188	0.221	0.381	0.453	0.427	0.241
9	SAM	0	0.191	0.214	0.227	0.253	0.326	0.236	0.246	0.187	0.222
10	YOA	0	0.133	0.230	0.255	0.269	0.262	0.383	0.262	0.241	0.227
11	MOM	0	0.136	0.135	0.389	0.230	0.128	0.102	0.097	0.088	0.1534
12	ALA	0	0.093	0.074	0.162	0.117	0.104	0.088	0.112	0.091	0.107
Mean		0	0.204	0.217	0.233	0.248	0.249	0.273	0.306	0.291	0.309
SD		0	0.074	0.086	0.078	0.089	0.096	0.098	0.118	0.125	0.174
C.V.,%		0	36.11	39.50	33.68	35.77	38.75	35.91	38.39	43.10	56.47

Table: (4.9): Plasma concentrations (µg/ml) of MT33 after oral administration to twelve healthy male volunteers

Sub. No	Sub. ID	Zero time	0.5 hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	24 hrs
1	MAH	0	0.373	0.3176	0.32	0.3127	0.2435	0.391	0.3128	0.4204	0.3972
2	KHN	0	0.2984	0.369	0.3147	0.363	0.3477	0.3986	0.3061	0.3167	0.3428
3	MOH	0	0.4332	0.4704	0.4516	0.4432	0.393	0.3838	0.2996	0.2958	0.4114
4	ABA	0	0.4221	0.4292	0.5154	0.4519	0.463	0.4959	0.4849	0.4987	0.4883
5	ABH	0	0.266	0.2998	0.2973	0.4059	0.3289	0.3793	0.416	0.3648	0.3693
6	MOA	0	0.1492	0.1936	0.1652	0.1828	0.1632	0.2124	0.2631	0.3748	0.5274
7	MOR	0	0.209	0.2097	0.2391	0.2926	0.2333	0.2435	0.3507	0.2352	0.292
8	MMO	0	0.2412	0.2604	0.2693	0.2657	0.2964	0.2545	0.2734	0.2666	0.2864
9	SAM	0	0.3276	0.3127	0.3462	0.3408	0.3532	0.3113	0.3409	0.3511	0.5356
10	YOA	0	0.0939	0.1003	0.3394	0.359	0.3709	0.4366	0.3641	0.3462	0.3418
11	MOM	0	0.1325	0.1273	0.1202	0.1014	0.1138	0.1507	0.1442	0.1389	0.3424
12	ALA	0	0.1678	0.1569	0.1823	0.2023	0.1737	0.1928	0.2147	0.39	0.2054
Mean	-	-	0.2594	0.2705	0.29	0.3101	0.2900	0.3208	0.3142	0.3332	0.3783
±SD	-	-	0.1138	0.1174	0.1138	0.1074	0.1053	0.1087	0.0891	0.0929	0.1001
C.V.,%	-	-	0.0939	0.1003	0.1202	0.1014	0.1138	0.1507	0.1442	0.1389	0.2054

Table (4.10): ANOVA of mean (± SD) plasma concentration (μg /ml) of Voltaren retard (100 mg) and MT33 at each sampling time after oral administration:

Time Hr/s	Voltaren retard 100mg	MT33	ANNOVA* NS**
Zero	0	0	
0.5	0.20±0.07	0.26±0.11	0.176
1	0.22±0.09	0.27±0.12	0.212
2	0.23±0.08	0.30±0.11	0.125
4	0.25±0.09	0.31±0.11	0.138
6	0.25±0.10	0.29±0.11	0.316
8	0.27±0.10	0.32±0.11	0.275
10	0.31±0.12	0.31±0.09	0.855
12	0.29±0.13	0.33±0.09	0.355
24	0.31±0.17	0.41±0.10	0.243
Minimum	0.20	0.26	-
Maximum	0.30	0.41	-
CV%	0.38	0.38	-

Table (4.11): Pharmacokinetic parameters of Diclofenac sodium after oral administration of Voltaren retard (1oo mg) to twelve healthy male volunteers

No	ID	AUC_{0-t} µg.hr/ml	$AUC_{0-\infty}$	C_{max} µg/ml	T_{max}	K_{el}	$T_{1/2}$
1	MAH	9.15	40.74	0.458	24	0.0145	47.79
2	KHN	10.96	42.51	0.6247	24	0.0198	35
3	MOH	8.53	33.49	0.5092	24	0.0204	33.97
4	ABA	6.9	76.28	0.4149	10	0.0046	15.065
5	ABH	8.14	27.13	0.4162	6	0.0211	32.84
6	MOA	4.8	19.57	0.2306	12	0.0133	52.11
7	MOR	5.26	14.91	0.3766	8	0.0168	41.25
8	MMO	8.18	61.51	0.4529	12	0.008	86.63
9	SAM	5.45	13.67	0.3256	8	0.0228	30.39
10	YOA	6.74	40.66	0.3825	10	0.0021	33
11	MOM	7.99	18.32	0.389	4	0.0085	81.53
12	ALA	2.61	3.52	0.117	6	0.1	6.93
Mean		7.06	30.42	0.3914	11.5	0.02099	41.38
$\pm$ SD		2.254	21.094	0.129	7.426	0.0258	23.461
Minimum		2.61	3.52	0.117	4	0.0021	6.93
Maximum		10.96	76.28	0.6247	24	0.1	86.63
C.V., %		31.93	69.34	32.96	64.57	122.92	56.7

Table (4.12): Pharmacokinetic parameters of Diclofenac sodium after oral administration of MT33 to twelve healthy male volunteers

No	ID	AUC_{0-t} (µg.hr/ml)	$AUC_{0-\infty}$	C_{max} µg/ml	T_{max} hrs	K_{el}	T1/2
1	MAH	8.66	93.17	0.4204	12	0.0047	14.74
2	KHN	7.93	59.87	0.3986	8	0.0066	16.5
3	MOH	8.72	23.68	0.4704	1	0.0275	25.2
4	ABA	11.41	28.269	0.4987	12	0.0018	38.5
5	ABH	8.57	37.787	0.416	10	0.01	69.3
6	MOA	7.99	26.5	0.5274	24	0.0285	24.32
7	MOR	6.21	22.43	0.367	10	0.018	38.5
8	MMO	6.42	54.15	0.2964	6	0.006	115.5
9	SAM	8.95	24.17	0.5356	24	0.0352	19.69
10	YOA	8.14	31.887	0.4366	8	0.0011	63.09
11	MOM	4.35	8.9	0.3424	24	0.0752	39.22
12	ALA	5.96	9.81	0.39	12	0.0534	12.98
Mean		7.78	35.05	0.4	12.58	0.0192	39.8
$\pm$ SD		1.82	23.78	0.07	7.54	0.023	29.991
Minimum		4.35	8.9	0.2964	1	0.001	12.98
Maximum		11.41	37.787	0.5274	24	0.0752	115.5
C.V., %		23.39	67.85	17.5	59.94	119.79	75.35

Table (4.13): Summary Statistics of the pharmacokinetic parameters of Diclofenac sodium after oral administration of Voltaren retard (100mg) to twelve healthy male volunteers

Period 1

Variable	N	Mean	± SD	Minimum	Maximum	C.V.,%
AUC_{0-t} (µg.hr/ml)	6	8.08	1.905	4.8	109.6	23.589
$AUC_{0-\infty}$ (µg.hr/ml)	6	39.95	18.021	19.57	76.28	45.104
C_{max}	6	0.44	0.118	0.23	0.62	26.792
T_{max}	6	16.67	7.54	6	24	45.255
K_{el}	6	0.016	0.0057	0.0046	0.021	36.825
$T_{1/2}$	6	36.13	11.91	15.06	52.11	32.979

Period 2

Variable	N	Mean	± SD	Minimum	Maximum	C.V.,%
AUC_{0-t} (µg.hr/ml)	6	6.038	2.078	2.610	8.180	34.416
$AUC_{0-\infty}$ (µg.hr/ml)	6	25.432	21.509	3.520	61.510	84.577
C_{max}	6	0.341	0.116	0.117	0.453	34.296
T_{max}	6	8	2.828	4	12	36.053
K_{el}	6	0.026	0.036	0.002	0.1	130.572
$T_{1/2}$	6	46.622	31.217	6.93	86.63	66.958

Table (4.14): Summary Statistics of the pharmacokinetic parameters of Diclofenac sodium after oral administration of MT33 to twelve healthy male volunteers

Period 1

Variable	N	Mean	± SD	Minimum	Maximum	C.V.,%
AUC_{0-t} (µg.hr/ml)	6	8.88	1.285	7.93	11.41	14.479
$AUC_{0-\infty}$ (µg.hr/ml)	6	44.879	27.090	23.68	93.17	60.368
C_{max}	6	0.455	0.050	0.3996	0.527	11.325
T_{max}	6	11.167	7.494	1	24	67.114
K_{el}	6	0.013	0.01178	0.0018	0.0285	89.403
$T_{1/2}$	6	31.426	20.371	14.74	69.30	64.822

Period 2

Variable	N	Mean	± SD	Minimum	Maximum	C.V.,%
AUC_{0-t} (µg.hr/ml)	6	6.672	1.644	4.35	8.95	24.64
$AUC_{0-\infty}$ (µg.hr/ml)	6	25.225	16.697	8.90	54.15	66.1969
C_{max}	6	0.3946	0.0834	0.2964	0.5356	21.137
T_{max}	6	14	8	6	24	57.143
K_{el}	6	0.0315	0.0288	0.0011	0.0752	49.695
$T_{1/2}$	6	48.1633	37.3604	12.980	115.50	77.570

Table (4.15): T-test for equality of means using Ln values.

Variable	N	Formulation	Mean	± SD	Sig. P- value (2 tailed)
AUC_{0-24} (μg.hr/ml)	12	Control MT33	1.896 2.024	0.38 0.25	0.343
$AUC_{0-\infty}$ (μg.hr/ml)	12	Control MT33	3.240 3.355	0.83 0.68	0.714
C_{max}	12	Control MT33	1.008 0.870	0.43 0.18	0.318
T_{max}	12	Control MT33	2.353 2.295	0.59 0.86	0.849
K_{el}	12	Control MT33	4.295 4.439	0.95 1.33	0.763
$T_{1/2}$	12	Control MT33	3.545 3.463	0.69 0.68	0.773

Table (4.16): Independent sample test for MRT and clearance:

Parameter	N	Formulation	Mean	± SD	Sig. P (2 tailed)
MRT	12	Control MT33	3.366 4.034	1.9 2.2	0.428
Clearance	12	Control MT33	5.823 4.328	2.4 3.2	0.526

Table (4.17): Area Under the plasma concentration-time curve (AUC_{0-24}) (μg.hr/ml) of Diclofenac sodium after oral administration of Voltaren retard and MT33 to twelve healthy male volunteers

NO	ID	Voltaren Retard (A)	MT33 (B)	Voltaren Retard (A) *Ln data	MT33 (B) *Ln data
1	MAH	9.15	8.66	2.2138	2.1587
2	KHN	10.96	7.93	2.3943	2.0706
3	MOH	8.53	8.72	2.1656	2.1656
4	ABA	6.9	11.41	1.9315	2.4345
5	ABH	8.14	8.57	2.0968	2.1482
6	MOA	4.8	7.99	1.5686	2.0782
7	MOR	5.26	6.21	1.6601	1.8262
8	MMO	8.18	6.42	2.1017	1.8594
9	SAM	5.45	8.95	1.6956	2.1917
10	YOA	6.74	8.14	1.9081	2.0968
11	MOM	7.99	4.35	2.0782	1.4702
12	ALA	2.61	5.96	0.9594	1.7851
Mean		7.06	7.78	1.9	2.0234
$\pm$ SD		2.25	1.82	0.3674	0.2399
Minimum		2.61	4.35	0.9594	1.472
Maximum		10.96	11.41	2.3943	2.1917
C.V., %		31.93	23.39	19.315	11.856

Table (4.18): Area under the plasma concentration – to infinity time curve ($AUC_{0-\infty}$) (μg.hr/ml) of Diclofenac sodium after oral administration of the control and drug brand to twelve healthy male volunteers

NO	ID	Voltaren Retard (A)	MT33 (B)	Voltaren Retard (A) *Ln data	MT33 (B) *Ln data
1	MAH	40.74	93.17	3.7072	4.5344
2	KHN	42.51	59.87	3.75	4.922
3	MOH	33.49	23.68	3.5112	3.1646
4	ABA	76.28	28.269	4.3344	3.3418
5	ABH	27.13	37.787	3.3006	3.632
6	MOA	19.57	26.5	2.974	3.2921
7	MOR	14.91	22.43	2.702	3.1104
8	MMO	61.51	54.15	4.1191	3.9918
9	SAM	13.67	24.17	2.6152	3.1851
10	YOA	40.66	31.887	3.7052	3.4622
11	MOM	18.32	8.9	2.908	2.1861
12	ALA	3.52	9.81	1.2585	2.2834
Mean		32.69	35.05	3.2405	3.3563
$\pm$ SD		21.094	23.78	0.792132	0.759865
Minimum		3.52	8.9	1.2585	2.1861
Maximum		76.28	37.787	4.3344	4.5344
C.V., %		69.34	67.85	24.4406	22.6380

Table (4.19): Peak plasma concentration (C_{max}) (µg/ml) of Diclofenac sodium after oral administration of Voltaren retard and MT33 to twelve healthy male volunteers

NO	ID	Voltaren Retard (A)	MT33 (B)	Voltaren Retard (A) *Ln data	MT33 (B) *Ln data
1	MAH	0.458	0.4204	0.78	0.84
2	KHN	0.6247	0.3986	0.47	0.92
3	MOH	0.5092	0.4704	0.67	0.75
4	ABA	0.4149	0.4987	0.88	0.7
5	ABH	0.4162	0.416	0.88	0.88
6	MOA	0.2306	0.5274	1.48	0.64
7	MOR	0.3766	0.367	0.98	1.05
8	MMO	0.4529	0.2964	0.79	1.22
9	SAM	0.3256	0.5356	1.12	0.62
10	YOA	0.3825	0.4366	0.96	0.83
11	MOM	0.389	0.3424	0.94	1.07
12	ALA	0.117	0.39	2.15	0.94
Mean		0.3914	0.4	1.01	0.87
$\pm$ SD		0.129	0.07	0.41665	0.174062
Minimum		0.117	0.2964	0.470	0.62
Maximum		0.6247	0.5274	2.150	1.22
C.V., %		32.96	17.5	41.3170	19.9039

Table (4.20): Analysis of variance of C_{max}

Parameter	Formulation	Mean	SD	p-value
C_{max}	VR	0.391	0.129	0.443*
	MT33	0.425	0.073	

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Table (4.21): Summary Statistics of the area under the plasma concentration-time curve (AUC_{0-24}) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	7.059	2.254	0.401
MT33	12	7.776	1.819	
Periods***				
Period 1	12	7.376	1.937	0.923
Period 2	12	7.459	2.217	

Table (4.22): Summary Statistics of the area under the plasma concentration – time curve ($AUC_{0-\infty}$) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	32.693	21.094	0.799
MT33	12	35.052	23.785	
Periods				
Period 1	12	32.589	19.053	0.782
Period 2	12	35.155	25.438	

Table (4.23): Summary statistics of peak plasma concentration (C_{max}) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	0.391	0.129	0.443
MT33	12	0.425	0.073	
Periods				
Period 1	12	0.418	0.107	0.639
Period 2	12	0.398	0.105	

Table (4.24): Summary statistics of time to peak plasma concentration (T_{max}) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	12.333	7.426	0.936
MT33	12	12.583	7.537	
Periods				
Period 1	12	15.333	7.878	0.052
Period 2	12	9.583	5.648	

Table (4.25): Summary statistics of the elimination rate constant (K_{el}) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	0.021	0.026	0.894
MT33	12	0.022	0.023	
Periods				
Period 1	12	0.024	0.022	0.708
Period 2	12	0.019	0.027	

Table (4.26): Summary statistics of the elimination half-life ($t_{1/2}$) for Voltaren retard and MT33

Formulation	N*	Mean***	SD	p-value**
Voltaren retard 100 mg	12	41.375	23.461	0.887
MT33	12	39.795	29.991	
Periods				
Period 1	12	42.146	27.411	0.779
Period 2	12	39.024	26.355	

Table (4.27): Time of peak plasma concentration (T_{max}) (Hrs) of Diclofenac sodium after oral administration of both Voltaren retard and test drug:

No	ID	Voltaren 100mg	Ln V.R	MT33	Ln MT33
1	MAH	24	3.178	12	2.4849
2	KHN	24	3.178	8	2.0794
3	MOH	24	3.78	1	0
4	ABA	10	2.3025	12	2.4849
5	ABH	6	1.7918	10	2.3025
6	MOA	12	2.4849	24	3.178
7	MOR	8	2.0794	10	2.3025
8	MMO	12	2.4845	6	1.7918
9	SAM	8	2.0794	24	3.178
10	YOA	10	2.3025	8	2.0794
11	MOM	4	1.3862	24	2.3025
12	ALA	6	1.7918	12	2.4849
Mean	-	12.33	2.512	12.58	2.5321
Minimum	-	4	1.3863	1	0
Maximum	-	24	3.178	24	3.178

Table (4.28): Elimination rate constant (K_{el}) of Diclofenac sodium after administration of VR and MT33 to twelve healthy male Volunteers

No	ID	Voltaren retard 100mg	Ln V.R	MT33	Ln T33
1	MAH	0.0145	4.23361	0.0047	5.36019
2	KHN	0.0198	3.92207	0.0066	5.02069
3	MOH	0.0204	3.89222	0.0275	3.59357
4	ABA	0.0046	5.3817	0.0018	6.31997
5	ABH	0.0211	3.85848	0.01	4.60517
6	MOA	0.0133	4.31999	0.0285	3.55785
7	MOR	0.0168	4.08638	0.018	4.01738
8	MMO	0.008	4.82831	0.006	5.116
9	SAM	0.0228	3.78099	0.0352	3.34671
10	YOA	0.0021	6.16582	0.0011	6.81245
11	MOM	0.0085	4.76769	0.0752	2.5876
12	ALA	0.1	2.30259	0.0534	2.92994
Mean	-	0.02099	3.86371	0.0192	3.95284
+ SD	-	0.0258	3.65738	0.023	-3.77226
Minimum	-	0.0021	6.16582	0.001	-6.90776
Maximum	-	0.1	2.30259	0.0752	-2.5876
C.V %	-	122.92	4.811534	119.79	4.78574

Table (4.29): Elimination half life ($t_{1/2}$) (hrs) of Diclofenac sodium after administration of VR and MT33 to twelve healthy male Volunteers

No	ID	Voltaren	Ln V.R	MT33	Ln MT33
1	MAH	47.79	3.8668	14.73	2.6899
2	KHN	35	3.5553	16.5	2.8034
3	MOH	33.97	3.5255	25.2	3.2268
4	ABA	15.07	2.7127	38.5	3.6507
5	ABH	32.84	3.4916	69.3	4.2384
6	MOA	52.11	3.9534	24.32	3.1913
7	MOR	41.25	3.7197	38.5	1.3807
8	MMO	86.63	4.4616	115.5	4.7493
9	SAM	30.39	3.4141	19.69	2.9801
10	YOA	33	3.465	63.09	4.1446
11	MOM	81.53	4.401	39.22	3.669
12	ALA	6.93	1.9356	12.98	2.5634
Mean	-	41.38	3.7228	39.8	3.6839
+ SD	-	23.46	3.1553	29.99	3.4009
Minimum	-	6.93	1.9359	12.98	2.5634
Maximum	-	86.63	4.4616	115.5	4.7492
C.V %	-	56.7	1.3957	76.35	4.3353

The mean plasma concentration following oral administration of MT33 (guar gum + gum Arabic) matrix tablet of Diclofenac sodium was shown in figure 4.9. Tmax of Diclofenac was 24±7.5 hrs and the peak concentration Cmax was 0.5274 ± 0.07 µg/ml which showed insignificant difference ($p>0.05$) compared to Voltaren retard tablets 0.624± 0.129. Tmax was 24±7.42 hrs ($p>0.05$).

4.5 Stability study results and discussion:

Diclofenac sodium contents from the different matrix tablets MT20, MT33, MT34, MT33p, and MT34p were presented as in the following tables (4.30- 4.36) after six months accelerated stability study.

Table (4.30): Initial readings of physical analysis of matrix tablets 10-07-2005

Formulae	Content (%)	Rt (Min.)	Peak area (mAU)	appearance	Disintegration
MT20	104	14.317	428.129	White flat tablet free from spots	Comply BP 2000
MT33	103	13.918	442.532	White flat tablet free from spots	Comply BP 2000
MT34	110	13.885	470.526	White flat tablet free from spots	Comply BP 2000
MT33p	97	14.333	416.900	White flat tablet free from spots	Comply BP 2000
MT34p	103	14.200	441.354	White flat tablet free from spots	Comply BP 2000

Table (4.31): First month content analysis of matrix tablets 10-08-2005

Formulation	Content (%)	Rt (Min.)	Peak area (mAU)
MT20	100.9	13.600	424.415
MT33	99.6	13.668	418.828
MT34	101.3	13.735	425.847
MT33p	103.7	13.683	435.999
MT34p	102.3	13.667	430.194

Table (4.32): Second month content analysis of matrix tablets 10-09-2005

Formulation	Content (%)	Rt(Min.)	Peak area (mAU)
MT20	97.9	13.683	405.609
MT33	98.7	13.683	408.844
MT34	96.7	14.217	400.683
MT33p	92.7	14.117	383.963
MT34p	92.2	13.800	381.961

Table (4.33): Third month content analysis of matrix tablets 10-10-2005

Formulation	Content (%)	Rt (Min.)	Peak area (mAU)
MT20	99.3	12.950	435.174
MT33	96.2	12.900	421.488
MT34	99.6	13.200	436.544
MT33p	96.7	13.127	423.823
MT34p	100.98	13.150	442.423

Table (4.34): Fourth month content analysis of matrix tablets 10-11-2005

Formulation	Content (%)	Rt (Min.)	Peak area (mAU)
MT20	99.0	13.000	433.725
MT33	96.0	12.950	422.254
MT34	100.0	12.900	422.254
MT33p	97.0	14.400	423.494
MT34p	102.0	14.433	449.623

Table (4.35): Fifth month content analysis of matrix tablets 10-12-2005

Formulation	Content (%)	Rt (Min.)	Peak area (mAU)
MT20	98.7	12.62	447.999
MT33	95.0	13.73	430.336
MT34	95.5	13.52	446.628
MT33p	98.4	13.58	443.714
MT34p	96.0	13.53	436.057

Table (4.36): Sixth month content analysis of matrix tablets 10-01-2006

Formulae	Content (%)	Rt (Min.)	Peak area (mAU)	appearance	Disintegration
MT20	96.2	14.017	423.437	White flat tablet free from spots	Comply BP 2000
MT33	95.0	13.800	417.233	White flat tablet free from spots	Comply BP 2000
MT34	94.0	13.600	412.588	White flat tablet free from spots	Comply BP 2000
MT33p	93.0	14.233	410.517	White flat tablet free from spots	Comply BP 2000
MT34p	93.0	14.133	409.388	White flat tablet free from spots	Comply BP 2000

Diclofenac sodium content from the different matrix tablets was presented in table 4.37. The average of analysis of three matrix similar formulations was 95-105 % (B.P limit).

Table (4.37) Summary of content: Diclofenac sodium Content from sample matrices:

No	Zero time	1st month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104±2%	101±1%	98±2%	99±0%	99±0%	99±2%	96±2%
MT33	103±1%	100±2%	99±3%	96±3%	96±3%	95±2%	95±1%
MT34	105±3%	101±1%	97±1%	100±1%	100±1%	96±1%	94±0%
MT33p	097±5%	104±2%	93±3%	97±2%	97±2%	98±1%	93±1%
MT34p	103±1%	102±0%	92±4%	101±2%	102±3%	96±1%	93±1%
STD	100%	100%	100%	100%	100%	100%	100%

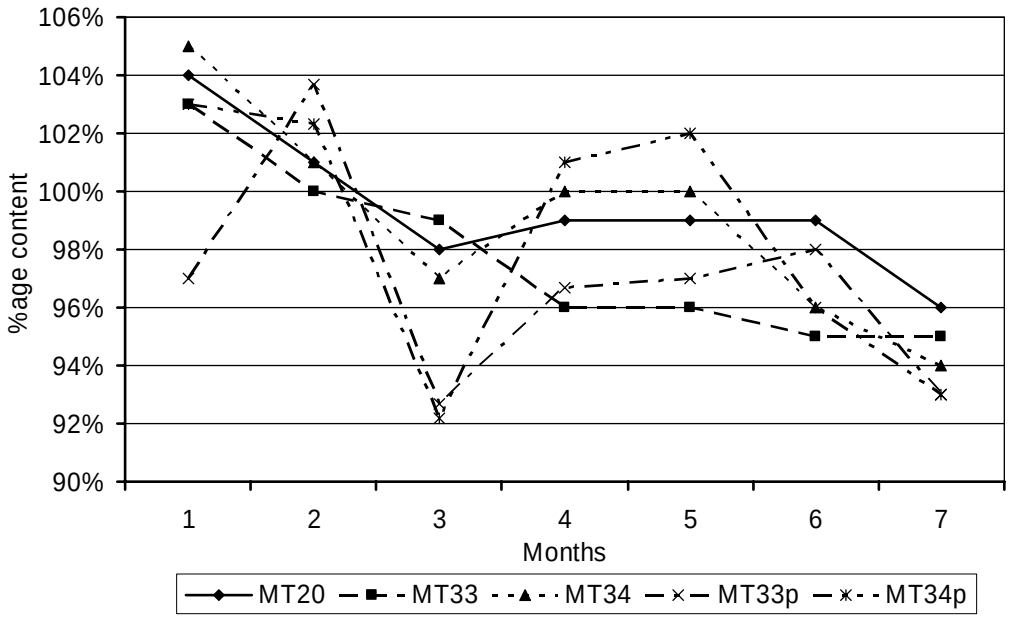

Figure (4.10): Stability profile of different Diclofenac formulae

Figure 4.10 shows the stability profile of the five preserved and non preserved tablet formulations. It was found to be between 90-105%. The two preserved formulae were out of the B.P limit after two months, while the other three formulae MT20, MT33p and MT34 were within the limit for five months. The two selected candidate formulas MT20 and MT33 were within the limit for the entire study time course which advocated their stability and expected reliability for use. Although the BP limit was 95% as the lower limit for stability study the 90% in MT33p and MT34p of the labeled potency were recognized as the minimum acceptable level (65), putting all the studied matrix tablets as passing the content requirements in the specified temperature and relative humidity (40C, and 75%RH) which agreed with Harpinder *et al* (75). No change in physical appearance, or organoleptic properties -color, odor and taste- was observed.

The stability of the Diclofenac sodium matrix tablets (MT20, MT33, MT34, MT33p, MT34p) was analyzed by the simple rule of thumb for out of trend stability study which stated that the out of trend (OOT) result is a stability result

that does not follow the expected trend, either in comparison with other stability batches or with respect to previous results collected during a stability study (PhRMA CMC statistics and stability expert team) (76).
The sample was considered out of trend if:

Rule one: Three of the consecutive results were outside some limit (BP).

Rule two: The result is outside $\pm$5%of the initial result.

Rule three: The result is outside $\pm$ 3% of the previous result.

Rule four: The result is outside $\pm$5% of the mean of all the previous results.

Table (4.38): Stability result from the application of rule one for matrix tablets

(+) complying (-) non-complying:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	+	+	+	+	+	+	+
MT33	+	+	+	+	+	+	+
MT34	+	+	+	+	+	+	-
MT33p	+	+	-	+	+	+	-
MT34p	+	+	-	+	+	+	-

Table (4.39): Stability result from the application of rule two for matrix tablets

(+) within the limit (-) out of the limit:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104	+	-	+	+	+	-
MT33	103	+	+	+	+	+	+
MT34	110	+	-	+	+	-	-
MT33p	097	+	+	+	+	+	+
MT34p	103	+	-	+	+	-	-

Table (4.40): Stability result from the application of rule three for matrix tablets

(+) within the limit (-) out of the limit:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104	+	+	+	+	+	+
MT33	103	+	+	-	+	+	+
MT34	110	-	-	+	+	-	+
MT33p	097	-	-	-	+	+	-
MT34p	103	+	-	-	+	-	-

Table (4.41): Stability result from the application of rule four for matrix tablets (+) within the limit (-) out of the limit:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104	101	+	+	+	+	+
MT33	103	100	+	+	+	+	+
MT34	110	101	+	+	+	-	-
MT33p	097	104	+	+	+	+	+
MT34p	103	102	-	+	+	+	-

4.6 Conclusion.

This study showed that combinations of guar gum plus gum Arabic, gum Arabic plus Xanthan, and HPMC plus Eudragit L100, in specific proportions could be used in matrix controlled release tablets prepared by direct compression.

From the in vitro release at pH1.2 for 2 hours and pH7.2 for 8 hours consecutively and from the physical properties the best controlled release formula was MT33 (guar gum 15% plus Gum Arabic 15%). MT20, MT33 and MT34 had significant correlation at the 0.01 level (2tailed) compared to Voltaren retard (table 16). MT33 compared with Voltaren retard showed significant regression coefficient (0.703) with sig. of (0.014) within the released time (table 4.1).

All the three matrices MT20, MT33, and MT34 were pH sensitive with zero-order release at pH 7.2.

Analyzing the above oral controlled delivery systems (MT20, MT33, MT34) using C8 method, precise and accurate results were obtained compared to C18 column. The precision which was less in C8 than C18 was abstracted from the standard deviations (SD) and relative standard deviations (RSD) table (4.2,4.3).

In this 100mg Diclofenac tablet which weighed about 165mg, the upper and lower permissible limits for content analysis were $\pm$7.5 % according to international standards (10). This agrees with the results obtained using C8 and C18 columns.

From table (4.4), the standard deviations were 2.07and 5.06, and relative standard deviations were 2.07and 4.92 respectively. Based on t-test no significant difference was found between contents measurement using C8 and C18 columns at p′-value of 0.05. (Observed t-value was 0.062 compared to the theoretical value of 2.15). The confidence of interval of the difference of the mean was - 0.58 to 0.16.

The retention time using C8 was almost double (13.7 minutes) the retention time using C18 column (8.0 minutes). This showed that the method of using C18 was advantageous over the BP 2000 method, since it was time sparing and was as similar as C8 method with no significant difference of content measurement.

Bio-equivalence of MT33 which is controlled release formula containing Diclofenac sodium with specified (15%) amount of guar gum and gum Arabic as matrix tablets was compared with Voltaren retard a well known Diclofenac

sodium which has controlled release action. No significant difference between the two formulations was observed. The rate and extent of absorption was almost the same with higher minimum effective concentration of MT33 formula at all the course interval of test up to 24 hours (Tables 4.6, 4.7, 4.8). The bio- equivalence was determined from ratios of test /control peak plasma concentration (Cmax) which equals 107.6% and area under the curve (AUC0-24) which equals 110.16% complying with the standard 90-125%.

The stability profiles of the controlled release matrices (MT20, MT33, MT34, MT33p, and MT34p) were found to be between 90-105%. The two preserved matrices (MT33p, and MT34p) showed one reading out of the BP limit at the second and another one at six month , while the other two formulae MT20, MT33 were within the BP limit (95-105%) for six months which advocated their stability and expected reliability for use. MT34 was out of limit at the six month.

From the application of out of trend stability rules (tables 4.38 – 4.41), it has been found that MT33 which contains guar gum 15% and gum Arabic15 % as controlled matrix was the best formula. The second one was MT20 which contains Eudragit L100 6% and HPMC 20 %. No

change in physical appearance, or organoleptic properties (colour, door and taste) was observed.

No microbiological growth (bacteria or fungi) was observed during a six month accelerated stability study in both preserved and non preserved matrices. This excludes the effect of preservation in these controlled release matrix delivery systems.

References

1/ Roseman, T. and Cardenelli, N. (1980). Controlled release technologies Vol1 (A.F. Kydonieus, Ed) CRC Press, Boca Ranton FL.

2/ Donald, L. (2000). Handbook of pharmaceutical controlled release Technology. Edited By Cambridge Scientific Inc. Cambridge Massachusetts Marcel Decker Inc. 465-503

3/ Sandeep Kumar and S.N. Sharma. (1991). Controlled release dosage forms. The Eastern pharmacist September, 17-21.

4/ Krishnaiah YSR, Seetha Devis A, Nageswara, Raot L, Bhshar Reddy PR, Karthikeyan RS, and Satyanarayana V, (2001). J. Pharm. Pharmaceut Sci 4(3): 235-243

5/ Roseman, T. J; cardinelli, N. F; (1980) in controlled release technologies vol. 11 (A.F. Kydonieus, ed) CRC Press Boca Ranton FL.

6/ Silvina A. Bravo, Maria C. Lamas, and Clandio J. Salpmon (2002). In vitro Studies of Diclofenac Sodium Controlled-Release from Biopolymeric hydrophilic Matrices, J. Pharm. Pharmaceut. Sci 5(3): 213-219.

7/ Krowczynsky L. (1987). Extended Release Dosage Forms, CRC Press, Boca Raton FL.

8/ Chien Y.W; (1992) Novel drug delivery systems 2nd Ed; Marcel Decker Inc, New York.

9/ Ravi Kumar, M.N.V., and Kumar N. (2001). Polymeric controlled Drug-Delivery systems, Perspectives Issues and Opportunities . Drug Der. Ind Pharm, 27: 1- 30.

10/ Herbert A. Lieberman, Leon Lachman, and Joseph B. Schwartz (1990). Pharmaceutical dosage forms Tablets Vol. 3 Marcel Decker Inc 270 Madison Avenue New York.

11/ Baul Steward. (1995). Review of Pharmaceutical controlled release methods and devices by Nottingham Trent University PhD thesis.

12/ Hendeles, L; Iafrate, R. P and Neinberger M., (1984). Clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. Clin. Pharmacokinetics. 9: 95-135.

13/ Dr. J.K. Lalla (1991). Introduction to controlled release and oral controlled drug delivery systems. The eastern pharmacist-September: 25-27.

14/ Colombo, P., (1993). Swelling controlled release in hydrogel matrices for oral route. Adv. Drug Del Rev 11: 37-57.

15/ Sung, K.C; Nixon, P. R; Skong, J. W; Ju, T.R; Gao. P.; Topp, E.M; and Patel, W.V. (1996). Effect of Formulation Variables on drug and polymer Release from HPMC-base Matrix Tablets. Int. J.pharm, 142 : 53-60.

16/ Ford, J.L.; Mitchell, K.; Rowe P.; Armstrong. D.J.; Elliot, P.N.C; Rostron, C; and Hogan, J.E. (1991). Mathematical modeling of drug release from hydroxymethylcellulose matrices: Effect of the temperature. Int. J Pharm. 71: 95-104.

17/ Decoursin, J. W., (1985). Conference Proceedings of the latest developments in drug delivery systems, Aster publishing corp. 29-32.

18/ Sheth P R. and Tossounian J.J., (1984). Drug Dev. Ind. Pharma, 10: 313-339.

19/ Md. Selim Reza, Mohiuddin Abdul Qaudir, Syed shabbir Haider (2003). Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J. Pharm. Pharmaceut. Sci., 6(2): 274-291.

20/ Vinayagam Kannan, Raghupathi Kandarapu, and Sanjay Garg. (2003). Optimization Techniques for the Design and Development of Novel Drug delivery Systems, Part II. Pharmaceutical Technology. March: 102-118.

21/ Ali Rajabi-Siaboomi. (2003). An Overview of Current Oral Modified Release Technologies. Business Briefing: Pharmatech, 181-184.

22/ Sandip B. Tiwari, T. Krishna Murthy, M. Raveendra Pai, Pavak R. Mehta and Pasula B. Chowdary, (2003). Controled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix Systems. PharmaSciTech May 14, Vol 04, issue 03 article: 31, 1-12.

23/ Rani M. Mishra B., (2004). Comparative In Vitro In Vivo Evaluation of Matrix, Osmotic Matrix, and Osmotic pump Tablets for Controlled delivery of Diclofenac Sodium. Aaps PharmSciTech. Auguest 20, Vol, 05, issue 04, article: 71: 1-10

24/ Michael H. Stephen T. and Cathy F., (2003). Oral Delivery of Poorly Soluble Drugs, Part 2: Formulation strategies for Solid Dosage forms and Novel Delivery Systems for Controlled Release. Pharmaceutical Manufacturing and Packing Sourcer (PMPS). Autumn, 21-24.

25/ Al-Saidan SM, Krishnaiah YS, Patro SS, Satyanaryana V. (2005). In Vitro and In Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled release of Water-soluble Diltiazem Hdrochloride. aaps PharSciTech. July 14, Vol. 06(01): 1-17.

26/ Ketan A. Mehta, M. Serpil Kislalioglu, Wantanee Phuapradit, A. Waseem Malick, and Navnit H. Shah, (2002). Effect of Formulation and Process Variables on Matrix Erosion And Drug Release From a Multiunit Erosion Matrix of Poorly Soluble Drug, Pharmaceutical Technology, 26-34.

27/ Mukesh C. Gohel and Maulik K. Panchal, (2001). A Novel Mathematical Method for Quantitative Expression of Deviation from Zero-order Drug Release, pharmaceutical Technology September, 62-74.

28/ Bhagya K. Narayan and Krisann Hall (2003). Polyvinyl Acetate Applied to Controlled-Release Formulations, Pharmaceutical Technology, 34-37.

29/ Rajan K. Verma and Sanjay Garg. (2001). Current Status of Drug Delivery Technologies and Future Directions, Pharmaceutical Technology, February 25(2), 1-14.

30/ T.J. Durig, G.W. Skinner and W.W. Harcum, (2001). Compression and Drug Release Characteristics of Directly Compressible KLUCEL® Hydroxypropylmethylcellulose Controlled Release Matrix Systems, Hercule Incorporated Aqualon Division Hercules Plaza 1313 north Market Street Wilmington, DE 19894-0001(800) 345-0447 WWW.aqualon.com: 1-7.

31/ Ketan A. Mehta, M. Serpil Kislalioglu, Wantanee Phuapradit, A. Waseem Malick, and Navnit H. Shah, (2005). In Vitro Release Performance of Nifidipine in Dogs from a Novel EUDRAGIT® - Based Multi-Unit Erosion Matrix, Drug Delivery Technology, 1-8.

32/ Seyed Alireza Mortazavi, and Reza Aboofazeli, (2003). An Investigation into the Effect of Carbopols on the release of Propranolol HCL from Tablet Matrices, Iranian Jounal of Pharmaceutical Research: 23-27.

33/ D. Flick and K. Kolter (2003). Polyvinyl Acetate Dispersion Development of Sustained-Release Pharmaceutical dosage forms by Granulation and Tableting, Pharmaceutical Technology, October, 86-100.

34/ S. R. Parakh, A. V. Gothoskar, and M. T. Karad, (2003). A Novel Method for the Study of Water Absorption Rates by Swellable Matrices, Pharmaceutical Technology, May: 40-48.

35/ Garima Chawla, Piyush Gupta, Vishal Koradia, and Arvind K. Bansal, (2003). Gastro-retention A Means To Address Regional Variability in Intestinal Drug Absorption. Pharmaceutical Technology, July, 50-65.

36/ Kuksal A, Tiwary AK, Jain NK, Jain S. (2006). Formulation and In Vitro, In Vivo Evaluation of Extended-release Matrix Tablet of Zidovudine: Influence of Combination of Hydrophilic and Hydrophobic Matrix Formers, aaps PharmSciTech. 7(1) article 1: 1-17.

37/ Satish K. Nachaegari and Arvand K. Bansal, (2004). Co-processed Excipients for solid Dosage Forms, Pharmaceutical Technology, January, 52-64.

38/ Mukesh C. Gohel, Laxman D. Patel, Shital H. Bariya, Rikita K. Dave and Nehal H. Bariya, (2003). Development and Evaluation of A Multi-functional Directly Compressible Diluents Consisting of Brittle and Ductile Material, Pharmaceutical Technology December, 64- 70.

39/ Jean-Maurice Vergnaud, (1993). Controlled Drug Release of Oral Dosage Forms. Ellis Horwood Limited, Market Cross House, Cooper Street, Chichester, West Sussex PO 19 1EB England.

40/ Nandita G. Das and Sudip K. Das (2003). Controlled Release Oral Dosage Forms. Formulation Fill & Finish, 10-16.

41/ D. Chulia, M. Dole; and V Pourcelot: (1998). Powder technology and pharmaceutical Processes. Elsevier science B.V. 513-544.

42/ H. P. Rang, M.M. Dale and J.M. Rilter. (1995). Pharmacology Churchill Livingstone published by Laurence Hunter.

43/ New drugs Articles (1983). Published by the British. Medical journals by the British. Medical Association.

44/ Todd, P.A; Sorkin, E.M. (1988). Diclofenac Sodium; Reappraisal of its pharmacodynamic and pharmacokinetics Properties, and therapeutic Efficacy Drugs 35: 244 –285.

45/ James, E.F. Reynolds, Martin dale. (1996). The Extra Pharmacopoeia. Published by Royal pharmaceutical society of Great Britain.

46/ Novartis report Basic drug information, May 08, (1990). Ciba Geigy Limited Basle, Switzerland, and Central Drug Regulatory Affairs. Regulatory Product Range Support.

47/ Kydonieus, A. (1992). Treatise on controlled drug deliver Marcel Dekker, Inc.

48/ Svetlana,I; Milica, J; Zorica, D; Jelena,P; Slobodan, D. Petrovic; Ljiljana, S; and Biljan, S. (2003). Artificial Neural Networks in the Modeling and Optimization of Aspirin Extended Release Tablets with Eudragit L 100 as matrix Substance. PharmSciTech Vol: 04, Issue 01, Article: 09, 1-12.

49/ Bhagwat; Dileep; Baichwali; Anande.R (2003). Diehl, 11; Donald Pen west pharmaceutical, Co (Patterson NY) APP No 479465 Jan.7.2000. Pharmaceutical patents US patents 6,537,578 March 25.1-19.

50/ Giunchedi, P; Gavaini, E; Moretti, MDL; and Prisino, G. (2000). Evaluation of Alginate compressed matrices as prolonged Drug Delivery Systems aaps pharma Sci. Tech., 1 (3) article 19, 1-10.

51/ Nishiru, B; and Kah-Hay Yuen. (2000). Formulation Variables Affecting Drug Release from Xanthan Gum matrices at Laboratory Scale and Pilot Scale .Phrm Sci. Tech.Vol: 01, issue 04 Article: 30.

52/ Amaral, MH; Lobo, JMS; and Ferreira, DC. (2001). Effect of hydroxypropylmethylcellulose and hydrogenated Caster oil on Naproxen Release from Sustained Release Tablets .aaps Pharm. Sci Tec., 2(2): article 6pp1-11.

53/ Lacy, LF. Keene O. N Duqeushoy, (1994). J. Pharm Sci. Vol, 83, 212-215.

54/ Jaber Emami, and Naser Tavakoli. (2004). Formulation of sustained-release lithium carbonate matrix tablets: influence of hydrophilic materials on the release rate and in vitro-in vivo evaluation. J. pharm. Sci. 7 (3) 338-344.

55/ R Galinsky and S. Vensson (2000). Basic pharmacokinetics, in Remington: The Science and practice of pharmacy 20th edition. Mack publishing company, Eston, Pennsylvania, 1127.

56/ M. Gibaldi (1991). Pharmaceutics and Clinical Pharmacokinetics 4th edition, Philadelphia, p 146.

57/ B.P 2001 British Pharmacopoeia Commission, stationary office limited.

58/ Alfred Martin, (2001). Physical pharmacy 4th edition, Lippincott Williams and Wilkins, 351 West Camden Street, Baltimore Maryland USA.

59/ WHO working document QAS/04. 088(2004).

60/ Singh, Sarajit, (1997). pharmatimes, 29, pp29-42.

61/ Singh, Sarajit, (1997). East.pharm, 60(479), pp 41-42.

62/ Singh, Sarajit, (1998). East.pharm, 61(487), pp 43-48.

63/ WHO technical report, series, 863, (1996). World Health Organization, Geneva, Switzerland.

64/ Monika Bakashi, and Sarajit sigh, (2003). ICH Guidance in Practice Stress Degradation Studies on Metronidazole and development of a validated stability-indicating HPLC assay Method. Pharmaceutical Technology, Oct., 148-160.

65/ Kulkarni. G.T, (2004). Pharmaceutics. Http///www. Editorial.htm.

66/ Gargar A.A.A and M.A. Abdulkarim. (2006). In Vitro Diclofenac Sodium Release Profiles From Different Controlled Release Matrices. Omdurman Journal of pharmaceutical Sciences (OJPS) No 2,125-134.

67/ Kurup T.R.R (1981). The need and control of: Microbiological Quality in Pharmaceuticals. The eastern pharmacist, August, 53-69.

68/ Hemant Bhatani, T.T. Mariappan and Sarajit singh, (2003). Behavior of Uptake of Moisture by Drugs and Excipients under Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of Light Part II: Packaged and Unpackaged Ant tuberculosis Drug Products. Pharmaceutical technology, June, 44-52.

69/ Bp (1999). British Pharmacopoeia Commission, stationary office limited.

70/ Ritger, PL; and Peppas, NA. (1987). A Simple equation for description of solute release. 11 Fickian and anomalous release from Swellable Devices. J. Controlled release. 5: 37-42.

71/ ELT Anni B.M, and Tashtoush B.M. (2003). Effect of Micoenvironment pH of Swellable and Erodable Buffered Matrices on the Release Characteristics of Diclofenac Sodium. AAPS Pharm. Sci. Tech. 4(3) article 43,1-13.

72/ Higuishi, T. (1963). Mechanism of Sustained-action medication, theoretical analysis of rate of rate of release of Solid drugs Dispersed in Solid matrices J. Pharma Sci. 52:1145-1149.

73/ Huls group (rohm). (1986). Application Technology Sheet, Pharma polymers, basic info. 2.3/E Eudragit acrylic polymers for controlled release Rohm, a company of the Huls group Germany, .1-6.

74/ Siahi MR,Barazegar-jalali M, Monajjemzadeh F,Ghaggari F,And Azarmi S, (2005). Design And Evaluation of 1- and 3- layer Matrices of Verapamil Hydrochloride for sustaining Its Release. Aaps PharmSciTech6 (4), E6, 26-632.

75/ Harpinter Kaur, T. Mariappan, and Saranjit Singh (2003). Behavior of Uptake of Moisture by Drug and Excipients under Accelerated Conditions of Temperature and Humidity in the Absence and Presence of Light, Part III: Various Drug Substances and Excipients. Pharmaceutical technology December, 52-56.

76/ RhRMACMC Statistics and Stability Expert teams, (2003). Identification of Out-of-Trend Stability Results, a Review of the Potential Regulatory Issue and Various Approaches. Pharmaceutical Technology, April, 39-52.

Appendix I: Percentage release of Diclofenac sodium at pH 1.2.

Time (h)	MT33	MT20	MT34	V.R	√t(mins)
1	0.07	0.08	0.07	0.48	7.74
2	0.08	0.06	0.15	0.53	10.95
3	0.11	0.23	0.11	0.43	13.42
4	0.16	0.25	0.03	0.40	15.49
5	0.12	0.27	0.04	0.45	17.32
6	0.37	0.33	0.38	0.65	18.97
7	0.22	0.17	0.05	055	20.49
8	0.35	0.43	0.09	053	21.91

Appendix II: Percentage release of Diclofenac sodium at pH 2.1

Time (h)	MT33	MT20	MT34	V.R	√t (mins)
1	0.32	0.27	4.7	0.27	7.74
2	0.71	0.42	3.5	0.80	10.95
3	1.14	0.59	3.4	0.92	13.42
4	1.61	0.79	3.3	0.89	15.49
5	1.89	0.98	3.1	0.83	17.32
6	2.34	1.14	2.6	0.16	18.97
7	2.58	1.31	3.4	0.99	20.49
8	2.62	1.43	3.1	1.04	21.91

Appendix III: Percentage release of Diclofenac sodium at pH 4.2

Time (h)	MT33	MT20	MT34	V.R	√t (mins)
1	2.6	1.21	1.30	1.80	7.74
2	1.93	1.72	2.70	2.70	10.95
3	2.38	1.85	2.40	1.90	13.42
4	2.46	2.05	1.90	1.40	15.49
5	1.58	1.20	3.60	4.00	17.32
6	1.25	1.08	1.50	2.00	18.97
7	1.76	1.47	0.80	1.30	20.49
8	0.99	1.50	2.60	3.00	21.91

Appendix IV: Percentage release of Diclofenac sodium at pH 5.5

Time (h)	MT33	MT20	MT34	V.R	√t (mins)
1	6.2	27.93	25.65	12.8	7.74
2	11.91	50.64	49.96	14.41	10.94
3	16.87	55.01	57.46	15.21	13.42
4	21.74	57.31	63.19	16.27	15.49
5	26.33	58.21	65.61	17.17	17.32
6	31.67	59.41	67.70	18.28	18.97
7	45.51	60.11	68.54	19.68	20.47
8	44.34	60.66	69.59	20.54	21.91

Appendix V: Percentage release of Diclofenac sodium at pH 6.5

Time (h)	MT33	MT20	MT34	V.R	√t (mins)
1	45.25	43.69	101.34	23.39	7.74
2	65.12	94.11	-	32.73	10.95
3	74.07	97.77	-	40.08	13.42
4	84.38	100.85	-	48.92	15.49
5	87.48	-	-	55.83	17.32
6	90.78	-	-	62.96	18.97
7	100.03	-	-	69.38	20.49
8	96.00	-	-	74.58	21.91

Appendix VI: Percentage release of Diclofenac sodium at pH 6.7

Time (h)	MT20	MT33	MT34	V.R	√t (mins)
1	18.54	66.54	28.31	11.51	7.74
2	27.77	97.37	93.97	19.82	10.95
3	32.99	102.24	95.08	24.72	13.42
4	37.51	-	99.52	29.88	15.49
5	41.55	-	97.49	32.89	17.32
6	45.40	-	95.59	39.14	18.97
7	46.20	-	97.9	43.28	20.49
8	52.51	-	101.60	46.73	21.91

Appendix VII: Percentage release of Diclofenac sodium at pH 7

Time (h)	MT33	MT20	MT34	V.R	√t (mins)
1	6.17	13.90	7.61	12.04	7.74
2	13.37	23.89	16.31	22.49	10.95
3	23.21	32.82	26.21	30.96	13.42
4	33.63	40.73	35.35	39.21	15.49
5	42.58	48.02	43.84	45.21	17.32
6	50.46	54.37	52.41	56.78	18.97
7	56.33	60.09	61.19	61.06	20.49
8	62.01	66.04	67.33	65.48	21.91