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FABRICATION AND *IN VITRO* EVALUATION OF CHITOSAN MATRIX TABLETS OF DICLOFENAC ON COLON DRUG DELIVERY SYSTEM (CODES)

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ABSTRACT: The objective of this study is to fabricate and Evaluate Chitosan Matrix tablets of Diclofenac.The effect of various polymers like ethyl cellulose, cellulose acetate phthalate on the release of Diclofenac have been evaluated. Tablets were evaluated for physical and chemical parameters such as Hardness, Friability, Thickness, Weight variation, Drug Content uniformity and *invitro* release. All batches are complied physical and chemical parameters with in the U.S.P limit.*Invitro* release profile of Diclofenac with 3%HPMC polymer (FH2) Showed that 97% of the drug was released at the end of 12^{th} hr which is considered as optimized formulation. The tablets showed no significant change either in physical appearance or in dissolution pattern after storing at 40^0 c / 75% RH and
60^0 C / 80% RH for three months. The drug release data fit well to Higuchi equation, Peppas and Korsemeyer equation. The drug release was found to have swelling and diffusion.
Keywords: Colon drug delivery system, Diclofenac sodium, Chitosan

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage form normally dissolves in the stomach fluid, intestinal fluid and absorb from the regions of the GIT depends upon the
Physico- chemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in the conditions where the drug needs to be protected from the hostile environment of upper GIT because of low enzymatic reaction.[1] The increasing number of peptide and protein drugs being investigated demands the development of dosage forms which exhibit site-specific release. Site specific delivery of drugs to the receptor site has the potential to reduce side effects ant to increase pharmacological response. One of the seemingly interesting areas to target drugs through oral route for systemic drug delivery is the colon, the proximal part of the large intestine. The treatment of disorders of the large intestine such as irritable bowl syndrome, colitis, crohn's disease, colon cancer and infectious disease where it is necessary to attain a high concentration of the active agent may be efficiently achieved using colon specific delivery systems[2] (CODES).Conventional oral dosage forms are ineffective in delivering drugs to colon due to absorption or degradation of the active ingredient in the upper gastrointestinal tract (GIT).Various approaches have been used for targeting the drugs to colon including, formation of prodrug, multi coating time dependent delivery systems, coating with ph sensitive polymers, pressure dependent systems and systems formulated making use of biodegradable polymers in matrix type[3].
From these approaches, one of the best approach is embedded matrix type. In this type the embedded drug in polysaccharide matrices is released by swelling and by the biodegradable action of polysaccharides[4].
Diclofenac sodium is a non-steroidal anti inflammatory agent which is widely used in the long term therapy for rheumatoid arthritis. It's biological half life 1-2hrs and it produces side effects such as peptic ulceration and bleeding. Hence there is a potential need for controlled as well as site specific drug release[5].
Chitosan is a naturally occurring polycationic polymer obtained from the N-deacetylation of chitin, found in the exoskeleton of crustaceans and insects[6]. It is easily biodegradable bio compatible and has great ease of chemical modification[7]. It has also been investigated as a suitable polymer coating for oral delivery of protein\peptide drugs as well as immobilization delivery of living cells [8-11].

The present investigation was undertaken to fabricate the Chitosan-Diclofenac sodium matrix tablets and evaluate the physico- chemical parameters.

MATERIALS AND METHODS

Materials

The following materials were used: Diclofenac sodium (Sun Pharma, Mumbai),
Chitosan (medium viscosity grade, RansomChem. Co., Redmond, WA) Methocel, Cellulose Acetate Phathalate, Ethyl cellulose were obtained from Dow Chemicals, USA. Talc, Lactose and Magnesium stearate were obtained Merck KgaA, Darmstadt, Germany. All other chemicals and solvents used were of analytical grade.

Method:

Formulation of tablets

Matrix tablets of Diclofenac sodium with chitosan in different ratio (1:0.2, 1:0.3, 1: 0.4) were prepared by wet granulation method using

1) Ethyl cellulose 3% solution in chloroform
2) Cellulose acetate phthalate (CAP) 3% solution in acetone.
3) Methocel 3% solution in water.
4) Methocel 3% solution in dichloromethane: ethanol (50:50) separately as granulating agent as shown in table No:1

The Diclofenac sodium and Chitosan were mixed in a planetary mixer. Diclofenac and polymer mixture is granulated with granulating agent. Then the wet mass is passed through sieve # 10 and dried at $55^0c \pm 5^0c$ for 1hr.After drying the granules were passed through sieve # 20.The granules were lubricated with magnesium stearate and talc. Then this blend is compressed with manually operated single punch tablet machine (KORSCH
ERWEKA, Frankfurt, Germany) using concave punches.

EVALUATION OF TABLETS

A) PHYSICAL TEST:

Tablets were subjected to various physical tests which include weight variation
(AX, Shimadzu-corporation, Japan), Thickness (Mitutoyo corps, Japan), Hardness tester (Toyoko, Japan), Friability (Friabilator, H.Jurgens GmbH & Co, Breman, Germany) as per B.P official methods.

B) DISSOLUTION TEST:

In vitro release study was performed using USP <711> apparatus type II at 50rpm**.**
(ERWEKA, Frankfurt, Germany).The dissolution medium was 900ml of hydrochloric acid pH 1.2 for 2hrs and pH 7.4 phosphate buffer for remaining 10 hrs maintained at
37 ± 0.5^0c.The drug was evaluated by taking sample of 2ml (which was replaced with fresh medium) at predetermined time intervals and absorbance was measured (λ= 276nm)
after filtration and suitable dilution (UV Spectrophotometer 150-02, Shimadzu corporation, Kyoto, Japan).

C) SHORT TERM STABILITY STUDIES:

The Stability study was conducted for optimized formulation (FH2). The tablets were packed and kept for 3 months at 4^0C, 40^0C / 75% RH & 60^0C / 80% RH in a stability chamber (Osworld, Mumbai). At the interval of 15 days tablets were withdrawn and evaluated for physical properties like Appearance, Hardness, Diameter, Friability, Weight Variation and Content uniformity. *In vitro* drug release and assay were also carried out.

D) MECHANISM OF DRUG RELEASE:

Korsemeyer et al., (1983) desired a simple relationship which described drug release from a polymeric system eq 2: To find out the mechanism of drug release, the drug release data was fitted in Korsemeyer- Peppas model[12].

$M_t / M_\alpha = Kt^n$

$M_t / M\alpha$ is the fraction of drug released at time't,' K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanism.

E) DATA ANALYSIS:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate eq 1: describes the system where the drug release rate is independent of its concentration[13].

$C=k_0t$

Where $k_{0\ is}$ zero order rate constant expressed in units of concentration /time and t is the time.
The following plots were made; Cumulative % release Vs time (zero order kinetic model); Cumulative % release Vs square root of time **(**Higuchi model); log cumulative % of release Vs log time (Korsemeyer- Peppas model).

RESULTS AND DISCUSSION

I) Physico-chemical parameters of tablets

Weight variation was within the limit of B.P (±5%) and Hardness of the formulations ranged from 3.95-4.58 kg/cm^2. All formulations exhibited less than 1% friability. Actual values are given in table: 2 length and breadth was found fixed as per punch size and thickness was controlled as well to an average of 2.68 mm and S.D was found as little as 0.048. By holding the tablet weight and thickness constant, the surface area and volume were essentially fixed. All tablets contained 100mg ± 5% of Diclofenac as confirmed by assay procedure. Mean drug content value obtained was 98.72 S.D of 0.115 which was found satisfactorily within limits.

II) *Invitro* charecterization of CODES

In formulations FE1, FE2 and FE3 3% ethyl cellulose was used as granulating agent in different drug chitosan ratio. The total amount of drug release from theFE1,FE2 and FE3 formulations were found to be 70.58%,67.68% and 61.53% respectively.The maximum drug release in first two 2hrs for these batches is about 19%.This is due to the addition of ethyl cellulose. From 3 rd hr onwards pH 7.4 buffer was used and the release is considerable at the end of 12^{th} hr.
In FC1, FC2 and FC3 formulations 3% cellulose acetate phthalate was used as granulating agent in different drug chitosan ratio. The total amount of drug release from

theFC1, FC2 and FC3 formulations were found to be 70.58%, 67.68% and 61.53% respectively. The maximum drug release in first two 2hrs for these batches is about 14.89% for the all the batches.

In FH1, FH2 and FH3 formulations Hydroxy propyl methyl cellulose phthalate was used as granulating agent in different drug chitosan ratio. The total amount of drug release from theFH1, FH2 and FH3formulations were found to be 102.43%, 97.73% and 88.68% respectively.

The drug release in first two hours in acidic buffer appreciably retarded by the HPMC because chitosan hydrochloride. From 3rd hr the release was constantly maintained even though chitosan has very little gel forming ability.

In FHP1, FHP2 and FHP3 formulations HPMC phthalate was used as granulating agent. The total amount of drug release in these formulations found to 78.26%72.38%&67.85% respectively and maximum drug release in first 2hrs is 13.53%.

From these results it was observed that the presence of enteric polymer has greater influence over the release retardant ability of delivery system in acidic media.

Chitosan hydrochloride which has greater solubility in acidic media and ultimately reduces the ability of the system to retard the release in acidic media.

Based on the ability of enteric polymer to retard the acidic release can be arranged as

HPMCP> CAP>EC

EC is slowly dissolving polymer having low degree of solubility in both acidic and basic medium unlike enteric polymer such as HPMCP, CAP & EC to sustain the release in either media.

The release profile of FH2 having Chitosan in the ratio of 1:0.3 and prepared using Methocel 3% as granulating agent was found to have maximum release of 97.73% at the end of 12th hr. Hence the formulation FH2 fulfills the objective and present study as site specific delivery to colon.

CONCLUSION

Chitosan Matrix tablets of Diclofenac were prepared successfully using Methocel as polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation correspond best fit to Higuchi, Peppas and Korsemeyer model. The optimized formulation is controlled by a complex mechanism of swelling mediated diffusion and lesser extent by erosion.

Table 1: Composition of different formulations of Diclofenac matrix tablets

S.No	Drug:Chitosan ratio	Formulation code	Ingredients			
			Diclofenac Sodium(mg)	Chitosan (mg)	lactose (mg)	Granulating agent
1	1:0.2	FE-1	100	20	25.5	EC 3%
2	1:0.3	FE-2	100	30	15.5	
3	1:0.4	FE-3	100	40	5.5	
4	1:0.2	FC-1	100	20	25.5	CAP 3%
5	1:0.3	FC-2	100	30	15.5	
6	1:0.4	FC-3	100	40	5.5	
7	1:0.2	FH-1	100	20	25.5	HPMC 3%
8	1:0.3	FH-2	100	30	15.5	
9	1:0.4	FH-3	100	40	5.5	
10	1:0.2	FH P-1	100	20	25.5	HPMCP3%
11	1:0.3	FH P-2	100	30	15.5	
12	1:0.4	FH P-3	100	40	5.5	

Note: In all formulations Talc (2%) and Magnesium stearate (1%) were included.

Table 2: Physical and Chemical parameters of formulated Diclofenac Matrix tablets FH-2.

Weight variation (%) n = 20	Thickness (mm) n =20	Friability (%) n= 10	Hardness (kg) n=20	Drug content (%) n = 10
Mean= 148.7mg +1.13%, -2.49% S.D = 0.3815	Mean= 2.68 mm +3.14mm, - 2.12mm, S.D = 0.048	0.40% S.D = 0.01	Mean= 4.19kg +6.5kg, -4.5kg S.D = 0.015	Mean= 99.40% S.D = 0.115

S.D = Standard Deviation, + = Maximum, - = Minimum

Fig 1*: In vitro* release of Diclofenac Matrix tablets FH-2 by U.V analysis.

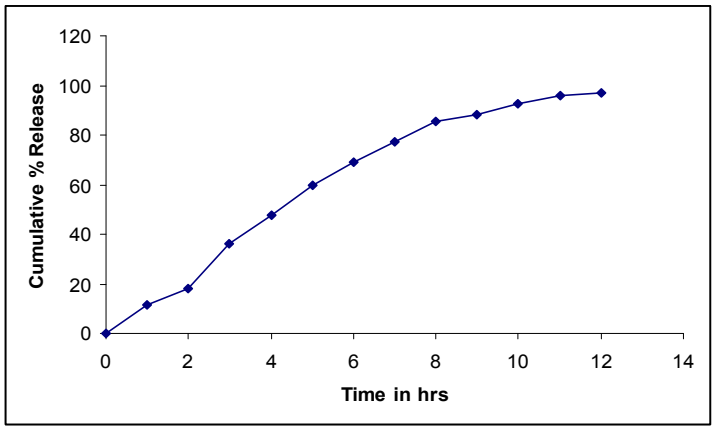
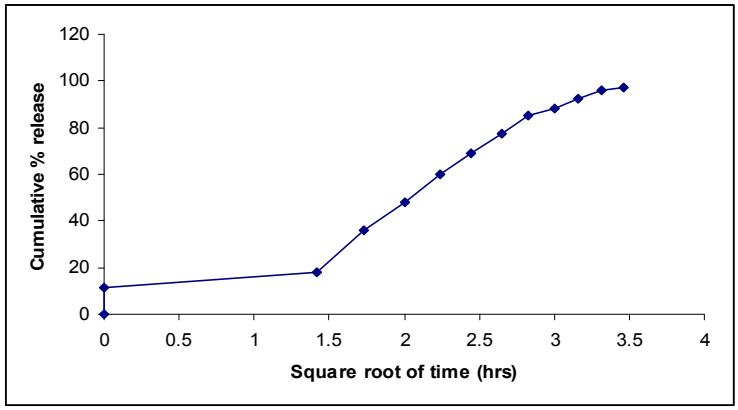
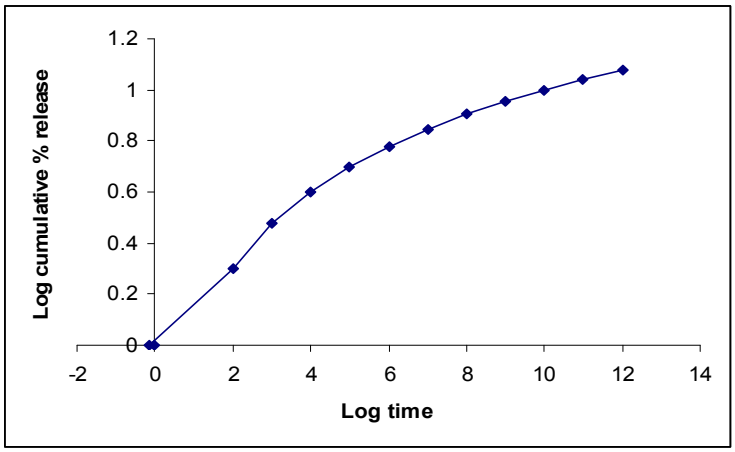


Fig 2: Higuchi release model of Diclofenac Matrix tablets FH-2.



Regression = 0.8916

Fig 3: Korsmeyer - Peppas model for mechanism of drug release Formulation FH-2.



Slope =0.9206

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