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A NOVEL APPROACH IN MODIFIED RELEASE DOSAGE FORMS FORMULATION AND EVALUATION OF ORAL CONTROLLED RELEASE MATRIX TABLETS OF ETODOLAC

P Sandhya[1*, 2], Siddiqua Habeeb[1], M Sunitha[1], KSK Rao Patnaik[2], CVS Subrahmanyam[3]

[1]Shadan Womens College of Pharmacy, Hyderabad, India.
[2]University College of Technology, Osmania University, Hyderabad, India.
[3]Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Hyderabad, India.

ABSTRACT

The objective of the present study was to develop extended release tablets of Etodolac 200mg. Etodolac tablets were prepared by direct compression method by using polymers like hydroxyl propyl methyl cellulose E-15, E-50, xanthan gum & guargum. The drug –excipient mixtures were subjected to preformulation studies. The tablets were subjected to physico chemical studies, in-vitro drug release, drug content studies. FTIR studies shown there was no interaction between drug & polymer. The physicochemical properties of tablets were found within limits. Etodolac is a non steroidal anti-inflammatory drug used in treatment of rheumatoid arthritis, osteoarthritis &analgesic. The drug release from optimized formulation was seen for 12 hours. The calculated regression coefficient showed higher R^2values with Higuchi models & zero order kinetics. It is clear through dissolution profiles of Etodolac matrix tablets prepared using different proportions of HPMC E50 that, this is a better controlled release polymer.

Key words: Extended release, Guar gum, HPMC E15, HPMC E50, Matrix tablets, Xanthan gum.

INTRODUCTION

In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficiency and patient compliance. Controlled release drug delivery systems [1] are those which deliver the drug at a pre-determined rate for maintaining a relatively constant, effective drug levels in the body for a specific period of time.

Polymers which are used as release retarding materials in the design of controlled release drug delivery systems (CRDDS) play a vital role in controlling the delivery of drug from these systems. The success of controlled release drug delivery systems depends on how well the polymer regulates the release of drug from the system.

In conventional drug therapy, a tablet provides only a single and transient burst of drug .It doesn't maintain drug blood level with in therapeutic range for extended period of time. The short duration of action is due to the inability of conventional dosage form to control the temporal delivery. As long as the amount of drug is above the minimum effective concentration, a pharmacological response is observed. Problems occur when the therapeutic range is very narrow or when the peak is beyond the upper limit of range. The other approach, multiple dose therapy also faces several potential Problems. If dose intervals is not appropriate for the biological half life of drug, large 'peak' & 'valleys' in the drug blood level may results. These Problems coupled with all dosage form to achieve spatial placement, is a compelling motive for investigation of controlled drug delivery systems [2].

It differs from sustained release systems which simply prolong drug release and hence plasma drug levels for extended period of time. Thus, the chief objective of most products should be controlled delivery to reduce dosing frequency to an extent that once daily dose is sufficient for therapeutic management through a uniform plasma concentration at steady state.

Corresponding Author :- **P.Sandhya** Email:- sandhyapasikanti@gmail.com

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Controlled Release Formulations

For conventional drug delivery systems, the rate limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastrointestinal wall. In sustained\controlled release product, one aims at the release of drug from the dosage form as rate limiting step instead. Thus drug availability is controlled by the kinetics of the drug release rather than absorption.

Controlled release drug delivery systems [3] are those which deliver the drug at a pre-determined rate for maintaining a relatively constant, effective drug levels in the body for a specific period of time.

Etodolac

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Etodolac Description

Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Its therapeutic effects are due to its ability to inhibit prostaglandin synthesis. It is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis [4]. Etodolac USP is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet contains Etodolac USP for oral administration. Etodolac USP is a racemic mixture of [+]S and [-]R-enantiomers. Etodolac USP is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide and aqueous polyethylene glycol.

Need for controlled release of Etodolac

Controlled release formulation is needed for Etodolac because of its short biological half-life of 4.0 hrs and also to minimize the gastro intestinal disturbances such as peptic ulceration with bleeding if present in larger concentration in gastro intestinal tract**.**

Oral controlled release systems

The oral route is most convenient and common mode for administration of controlled release systems.
Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible because of versatility of gastro intestinal anatomy and physiology) and ease of production and low cost of such a system. These systems have gained importance because of the technological advances made in fabrication, which help to achieve zero order release rates of therapeutic moiety.

The major types of controlled release systems intended for oral use are

1. Coated pellets.
2. Matrix tablets.
3. Ion exchange and complexation methods.
4. Micro encapsulation and microcapsules.
5. Osmotically controlled oral preparations.
6. Slow dissolving salts and complexes.
7. pH independent formulations.

Matrix Devices

A matrix device as the name implies, consists of drug dispersed homogenously throughout a polymer matrix [5].

Materials used as retardants in matrix tablet formulations

Matrix characteristics	- Materials
Insoluble, inert	- Poly ethylene, Ethyl cellulose,
Insoluble, erodible	- Carnauba wax, Stearyl alcohol, Stearic acid Hydrophilic,
Swellable	- Methyl cellulose (400cps, 4000cps) Hydroxyl ethyl cellulose.

Advantages of Matrix System

They are, in general, easy to make and can be made to release high-molecular weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur.

Disadvantages of Matrix System

The primary disadvantages of this system are the remaining matrix "ghost" must be removed after the drug has been released. Also, the release rates generated are not zero-order, since the rate varies with the square root of time

MATERIALS AND METHODS

Direct Compression

Direct compression comprises of compressing tablets from powdered material whose materials physical properties remaining unchanged. This method is well suited for compounds with drug content less than 30% of formulations [6-9]. It involves very few processing steps. The commonly used fillers in pharmaceutical solid dosage forms includes Dicalcium phosphate Dehydrate, Tricalcium phosphate, Calcium sulfate, Lactose anhydrous, Lactose spray-dried, Starch 1500, Mannitol, Microcrystalline cellulose, Compressible sugar.

RESULTS

Controlled release tablet were prepared by using natural gums xanthan gum, guar gum, hydroxyl propyl methyl cellulose at different drug to gum ratio, microcrystalline cellulose as diluent, povidone k30-tablet binder, magnesium stearate and talc as lubricant.

The weighed quantities of drug and gum were mixed thoroughly in different ratios 1:0.5, 1:1, 1:1.5 were

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prepared by direct compression technique. The tablets were evaluated for its pre compression parameters like Bulk density, Angle of response, True density, Hausner ratio and post compression parameters like Hardness, Friability, Uniformity of drug content, *in vitro* dissolution studies. Angle of repose was calculated for the powder and the powder was found to have excellent flow properties. The results are shown in table 3, 4 respectively.

All the tablets prepared contained Etodolac within 200±5% of the labeled claim.

Hardness and friability

As such the prepared tablets were of good quality with regard to drug content, hardness and friability [10-11]. Hardness and Friability of the tablets were within official (IP) limits. The Hardness of prepared controlled tablets of Etodolac was found to be in the range of 2.0 -5.5 kg /cm^2 and is given in table 4.The Friability of all the tablets was found to be less than 1%i.e in the range of 0.5-1% given in the table 4.

***In vitro* dissolution studies**

All the tablets were found to be non – disintegrating in water and aqueous fluids of acidic (1.2) and alkaline (7.4) pH. As the tablets formulated with various polymers were non – disintegrating with acidic and alkaline fluids, they are considered suitable for oral controlled release.

In vitro dissolution studies were performed for all the batches of Etodolac using USPXIII dissolution apparatus II at 50 rpm, 900ml dissolution media. The release data was shown in table .

Formulations F1, F2, F3 containing drug: guar gum ratio of 1:0.5, 1:1, 1:1.5 exhibited 89.33%, 71.21%, 68.39 % release in 7th, 12th hour respectively. Formulations F4, F5, F6 containing drug: gum ratio of xanthm gum 1:0.5, 1:1, 1:1.5 exhibited 77.24%, 66.66%, 60.08% release in 12th hour respectively.

Formulations F7, F8, F9 containing drug: gum ratio of HPMC E-15 in 1:1, 1:1.5 exhibited 98.82%, 98.32% release in 10th, 12th hour respectively.

Formulations F10, F11, F12, containing drug: gum ratio of HPMC E-50 1: 0.5, 1:1, 1:1.5 exhibited 98.32%, 88.27%, 74.80% release in 12th hour respectively. Etodolac release from all the tablets was slow and spread over longer periods of time [12-16].

From the above results it was observed that with increase in concentration of polymer, there is decrease in the drug release which may be attributed to increased viscosity of the gel as well as the gel layer with longer diffusional path. The drug release was relatively rapid in the case of HPMC E-15 and guar gum and the release was completed within 8 – 10 hours with these tablets. With HPMC E50 tablets the release was completed within 12 hours. Xanthan gum gave very slow release, 60.08% in 12 hours. The order of increasing release – retarding effect observed with various polymers was xanthan gum > HPMC E50 >guar gum > HPMC E-15. Thus HPMC E50 was found to be a better release – retarding polymer than HPMC E-15, xanthan gum, guar gum and could be used in the formulation of controlled release matrix tablets [17-19].

Drug release

Drug release from matrix tablets was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37±1°C. Phosphate buffer of pH 7.4 (900 ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 276 nm for etodolac using a Shimadzu UV-150 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate.

Data analysis

Release data were analyzed as per zero order, first order, Higuchi [21] and Peppas [22,23] models to assess the drug release kinetics and mechanism from the tablets prepared. The results are shown in table 5.

Fig 1. Plasma drug concentration profiles for conventional tablet or capsule formulation, a sustained release formulation and a zero order controlled release

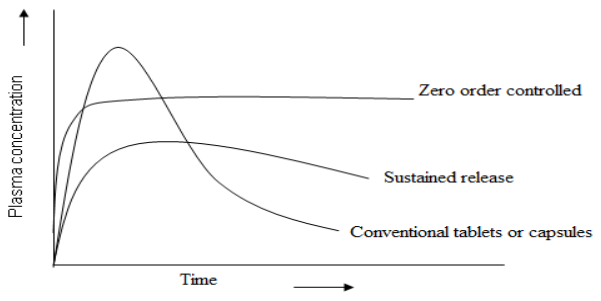

Fig 2. Drug Release Profile of F10 before and after Storage for 5 months at 40^0 C

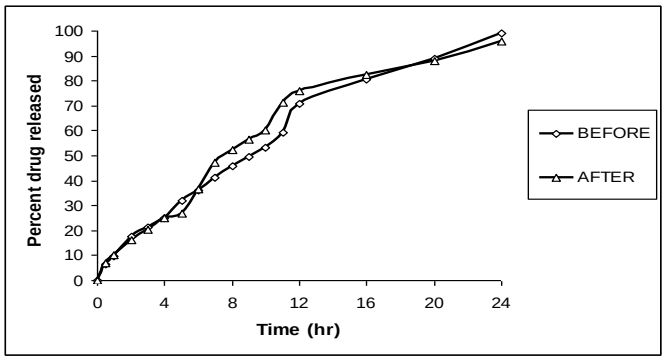

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Table 1. List of materials

Materials	Source
Etodolac	Bari pharmaceuticals
HPMC E-15	Bari pharmaceuticals
HPMC E-50	Bari pharmaceuticals
Guar gum	Bari pharmaceuticals
Xanthan gum	Bari pharmaceuticals
Talc	Bari pharmaceuticals
MCCpH101	Bari pharmaceuticals
Magnesium stearate	Bari pharmaceuticals

Table 2. Formulae of Etodolac matrix tablets prepared by various polymers

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Etodolac	200	200	200	200	200	200	200	200	200	200	200	200
Guar Gum	100	200	300	-	-							
Xanthum gum	-	-	-	100	200	300						
HPMCE-15	-	-	-	-	-		100	200	300			
HPMCE-50	-	-			-					100	200	300
Povidone K30	60	60	60	60	60	60	60	60	60	60	60	60
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Microcrystalline cellulose	216	116	16	216	116	16	216	116	16	216	116	16
Total weight(mg)	600	600	600	600	600	600	600	600	600	600	600	600

Table 3. Precompression parameters of the final blend

Formulation	Bulk density ($gm\backslash cm^3$)	Tapped density ($gm\backslash cm^3$)	Compressibility index	Angle of repose	Hausners ratio
F1	0.38	0.625	39.2	24^0	1.644
F2	0.31	0.625	50.4	24^0	2.016
F3	0.45	0.625	28	23^0	1.388
F4	0.37	0.600	38.33	20	1.689
F5	0.38	0.600	38.33	20.36	1.570
F6	0.37	0.600	38.33	21.56	1.570
F7	0.612	0.750	18.366	28.76	1.225
F8	0.609	0.760	19.86	27.35	1.321
F9	0.611	0.712	14.18	25.62	1.305
F10	0.742	0.833	10.92	20.35	1.27
F11	0.678	0.792	14.39	18.92	1.168
F12	0.596	0.748	20.32	19.76	1.289

Table 4. Post compression parameters of the tablets

Formulation	Weight variation	Hardness Kg/sq.cm	Thickness	Friability (%)	Disintegration Time (min)	Etodolac (mg/tab)
F	1.7%	3.0	4	0. 49	Non-disintg.	100.2
F2	1.5%	3.5	4	0.37	Non-disintg.	101.2
F3	3%	3.5	4	0.30	Non-disintg.	99.6
F4	2%	4.0	3.5	0.15	Non-disintg.	99.4
F5	1.5%	4.5	3.5	0.25	Non-disintg.	100.65
F6	3%	4.0	3.5	0.25	Non-disintg.	100.2
F7	2.3%	2.0	3	0.30	Non-disintg.	101.2
F8	3%	2.5	3	0.28	Non-disintg.	99.67
F9	1%	3.0	3	0.25	Non-disintg.	99.70
F10	1%	5.0	3	0.15	Non-disintg	101.65
F11	1.56%	5.0	3	0.10	Non-disintg	100.3
F12	2%	5.5	3	0.10	Non-disintg	100.78

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Table 5. Kinetic models for drug release of Etodolac

Formulation	Zero order model	First order model	Higuchi model	Peppas equation	Hixson crowell's
F1	0.972	0.669	0.974	0.44	0.851
F2	0.989	0.877	0.921	0.648	0.955
F3	0.979	0.877	0.905	0.572	0.942
F4	0.971	0.847	0.974	0.873	0.978
F5	0.986	0.966	0.946	0.859	0.987
F6	0.944	0.762	0.855	0.945	0.924
F8	0.981	0.596	0.986	0.524	0.872
F9	0.972	0.502	0.942	0.658	0.812
F10	0.981	0.612	0.988	0.783	0.830
F11	0.972	0.694	0.972	0.812	0.894
F12	0.976	0.777	0.945	0.765	0.930

Table 6. Drug Release Profile of F10 before and after Storage for 5 months at 40^0 C

Time (hr)	Percent Etodolac release from formulation F10	
	Before	After
0	0	0
0.5	6.54	6.818
1	9.5	10.31
2	17.61	16.30
3	21.21	20.51
4	24.99	24.87
5	31.72	26.99
6	36.29	36.66
7	41.15	47.09
8	46.20	50.36
9	49.34	56.38
10	53.34	60.4
11	59.45	67.07
12	70.81	71.07
16	80.57	82.38
20	89.57	87.75
24	99.06	97.06

CONCLUSIONS

Matrix tablets each containing 200 mg of Etodolac were formulated employing various polymer in different proportions of drug and polymer and the tablets were evaluated for hardness, friability, disintegration time and drug release kinetics and mechanisms. .Hardness and friability of the tablets were within official (IP) limits .The formulated matrix tablets met the pharmacopeia requirement of uniformity of weight. All the tablets confirmed to the requirement as per I.P. An evaluation of the drug release retarding efficiency of the HPMC E-50 in comparison to known polymers such as HPMCE-15, guar gum and xanthan gum was also made. For comparison drug release from Reactin SR tablets, a commercial sustained release formulation of Etodolac was also studied.

Etodolac tablets containing HPMC E-50, Povidone, MCC which are taken as ideal or optimized formulation of sustained release tablet for 12 hours release as it fulfills all the requirements of sustained release tablet and study encourages further clinical trials and long term stability study on this formulation.

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