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Research Paper

Preparation and Characterization of Ibuprofen Matrix Tablets Using Different Blends of Polymers

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Hydroxypropyl methyl cellulose and crystalline methyl cellulose are matrix polymer can be used in formulation of sustained (extended) release dosage form of slightly water soluble drug. It was decided to study the effect of the various polymer at different matrix polymer ratio, on release profile of drug from matrix formulation prepared using hydrophilic and hydrophobic matrix system and both matrix systems in different polymer ratio used. Ibuprofen was considered as ideal drug for sustained release formulation. In order to achieve required sustained release profile tablets were directly compressed using Crystalline Methyl Cellulose, HPMC, and Magnesium stearate in different- different ratio. The formulated tablets were also characterized by physical and chemical evaluation parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. The results of dissolution study showed that the Combination polymer (HPMC and CMC) of one Batches tablets show Better release rate as compared to another Batches tablets which having HPMC alone

Keywords : HPMC, CMC, Ibuprofen, Magnesium stearate.

INTRODUCTION

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24hrs into one tablet / capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations[2].

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Drug Properties, Which are Suitable for, Extended Release Formulation

a) Physiochemical Properties of the drug[1,3]

- Aqueous solubility: (>0.1mg/ml)
- Partition co-efficient: (1000:1 octanol: water system)
- Drug stability in vivo: (High enough, so drug remain stable during release from system)
- Protein binding: (Drug with high protein binding will not require release modification.
- Drug pKa & ionization at physiological pH: (pKa for acidic API= 3.0 - 7.5, pKa for Basic API = 7.0 - 11.0)

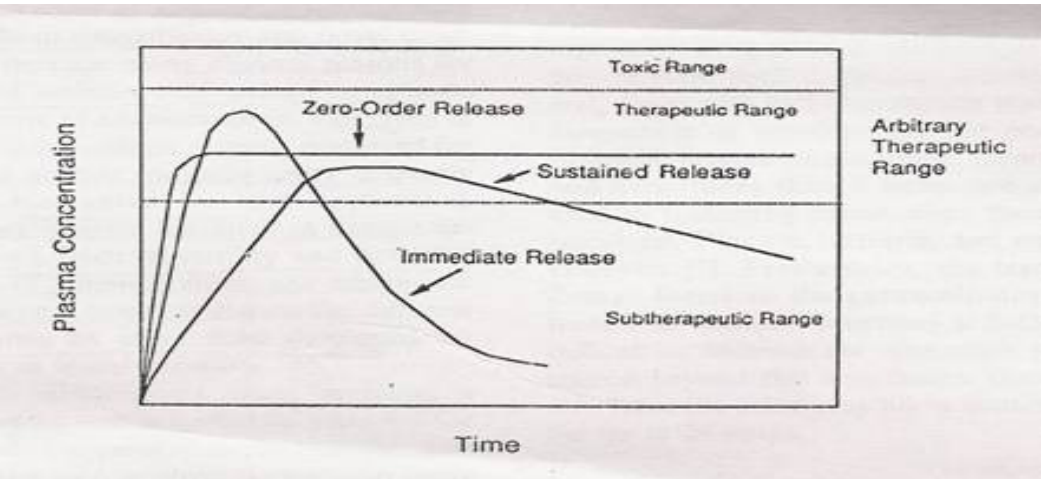

Fig. 1-Drug plasma levels after oral administration of a drug from an extended release dosage from.

- Mechanisms and sites of absorption: (Mechanism of absorption should not be active type and absorption window should not be narrow)
- Molecular size and diffusivity: (Moleculesize should be small (100-400 D so it canbe easily diffused through polymer matrix)
- Dose size: (<800mg)

b) Biological Properties of Drug[1,3]

- Distribution: (A.P.I. with large volume of distribution is not suitable).
- Metabolism: (A.P.I. should be metabolized with intermediate speed).
- Half-life of drug: (2 - 8 hrs).
- Margin of safety: (High enough so dose dumping does not cause any serious side effect).
- Plasma concentration response relationship: (A.P.I. having linear relationship is better candidate).

Extended Release Formulation Design-

1) Diffusion Sustained System

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. Diffusion process has been utilized in design of controlled release drug delivery systems for several decades. This process is a consequence of constant thermal motion of molecules, which results in net movement of molecules from a high concentration region to a low concentration region. The rate of diffusion is dependent on temperature, size, mass, and viscosity of the environment. Molecular motion increases as temperature is raised as a result of the higher average kinetic energy in the system[12].

$$\mathbf{E} = \frac{\mathbf{KT}}{\mathbf{2}} = \frac{\mathbf{mv^2}}{\mathbf{2}}$$

E = kinetic energy
k = Boltzmann's constant
T = temperature
m = mass
v = velocity

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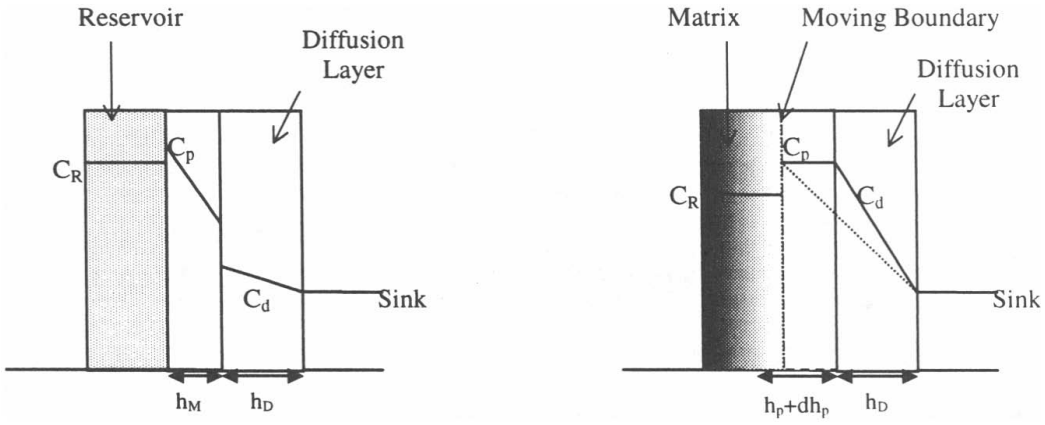

Fig. 2: Schematic illustrations of reservoir versus matrix systems

Mathematically, the rate of drug delivery in diffusion-controlled delivery systems can be described by Fick's laws. Fick's first law of diffusion is expressed as[12]

$$\mathbf{J} = -\boldsymbol{D}\frac{\boldsymbol{dC}}{\boldsymbol{dx}}$$

Where J = flux of diffusion

D = diffusivity of drug molecule

$\frac{dC}{dx}$ = concentration gradient of the drug molecule across diffusion barrier with thickness.

According to the diffusion principle, controlled-release drug delivery systems can be designed as a reservoir system or a matrix system. Drugs released from both reservoir and matrix type devices follow the principle of diffusion, but they show two different release patterns as shown in Fig. 2. In this Fig. CR is drug concentration in the reservoir or matrix compartment, Cp is solubility of Drug in the polymer phase, Cd is the concentration in the diffusion layer, hm is the thickness of the membrane, hd is thickness of the diffusion layer, and hp + dhp indicates the changing thickness of the depletion zone of matrix.

In a reservoir system, if the active agent is in a saturated state, the driving force is kept constant until it is no longer saturated. For matrix systems, because of the changing thickness of the depletion zone, release kinetics is a function of the square root of time. A typical reservoir system for transdermal delivery consists of a backing layer, a rate-limiting membrane, a protective liner, and a reservoir compartment. The drug is enclosed within the reservoir compartment and released through a rate-controlling polymer membrane. Membranes used to enclose the device can be made from various types of polymers. The rate of release can be varied by selecting the polymer and varying the thickness of the rate-controlling membrane. The drug in the reservoir can

be in solid, suspension, or liquid form[10].

1.1) Diffusion Reservoir System

In this system, a water insoluble polymeric material covers a core of drug.

Advantages

- Zero order delivery is possible.
- Release rates can be modified with polymer type & concentration.

Disadvantages

- Difficult to deliver high molecular weight compound.
- Generally increased cost per dosage unit.
- Potential toxicity if dose dumping occurs.

1.2) Diffusion matrix system

The matrix system is defined as a well-mixed composite of one or more drugs with partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism. The diffusion type reservoir system is shown in [13](**Fig. 3**).

Gelling agent i.e. hydrophilic polymers

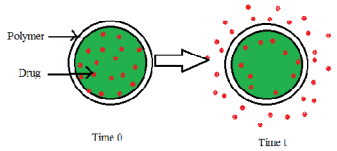

Fig. 3: Schematic representation of diffusion type reservoir system

Matrix systems are widely used for sustaining the release rate. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[8]. A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. The diffusion type matrix system is shown in (**Fig. 4**)[13].

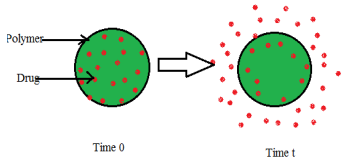

Fig.: 4 Schematic Representation of Diffusion Type Matrix System

Advantages:

- Easier to produce than reservoir or encapsulated devices.
- Versatile, effective and low cost.
- Possible to formulate high molecular weight compounds.
- Increased the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.

Disadvantages:

- The ghost matrix must be removed after the drug has been released.
- The release rates are affected by various factors such as, food and the rate transit through the gut. Cannot provide pure zero order release.

2) Dissolution Sustained Systems

Controlled release of drug can be achieved by utilizing the rate-limiting step in the dissolution process of a solid drug with

relatively low aqueous solubility. The dissolution rate can be quantitatively described by the Noyes-Whitney equation as follows.

$$\frac{dC}{dt} = \frac{DA}{h}(C0 - Ct)$$

Where $\frac{dC}{dt}$ = rate of drug dissolution

D = diffusion coefficient of drug in diffusion laye

h = thickness of diffusion layer

A = surface area of drug particles

$C0$ = saturation concentration of the drug in diffusion layer

Ct = concentration of drug in bulk fluids at time t

The surface area A of the drug particle is directly proportional to the rate of dissolution. For a given amount of drug, reducing the particle size results in a higher surface area and faster dissolution rate. However, small particles tend to agglomerate and form aggregates. Using a specialized milling technique with stabilizer and other excipients, aggregation can be prevented to make microparticles smaller than 400 nm in diameter to improve the dissolution of the drug in the body.

The saturation solubility C0 can also be manipulated to change the rate of dissolution. Both the physical and chemical properties of a drug can be modified to alter the saturation solubility. For example, salt forms of a drug are much more soluble in an aqueous environment than the parent drug. The solubility of a drug can also be modified when the drug forms a complex with excipients, resulting in a complex with solubility different from the drug itself.

Controlled or sustained release of drug from delivery systems can also be designed by enclosing the drug in a polymer shell or coating. After the dissolution or erosion of the coating, drug molecules become available for absorption. Release of drug at a predetermined time is accomplished by controlling the thickness of coating. In spansule systems, drug molecules are enclosed in beads of varying thickness to control the time and amount of drug release. The encapsulated particles with thin coatings will dissolve and release the drug first, while a thicker coating will take longer to dissolve and will release the drug at later time. Coating-controlled delivery systems can also be designed to prevent the degradation of the drug in the acidic environment of the stomach, which can reach as low as pH 1.0. Such systems are generally referred as enteric-coated systems. In addition, enteric coating also protects the stomach from ulceration caused by drug agents. Release of the drug from coating controlled delivery systems

may depend upon the polymer used. A combination of diffusion and dissolution mechanisms may be required to define the drug release from such systems.[16]

Dissolution system:

2.1) Soluble Reservoir System

In this system drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats as shown in (**Fig. 5**)[3].

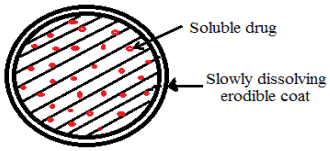

Fig. 5: Schematic Representation of Dissolution of Reservoir System

The maintenance dose of drug can be achieved by applying thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.[17]

2.2) Soluble matrix system

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. The more common type of dissolution sustained dosage form is shown in (**Fig. 6**)

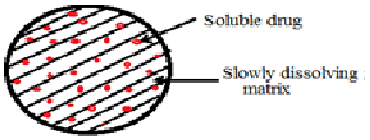

Fig. 6: Schematic Representation of Dissolution of matrix System

2.3) Dissolution- Sustained Pulsed Delivery System

Amongst Sustained release formulations hydrophilic matrix technology is the most widely used due to its following advantages.

- Provide desired release profile for a wide therapeutic drug category, drug and solubility.
- Simple and cost effective manufacturing and robust.
- Patient acceptance.
- Ease of drug modulation through level, choice of polymeric systems & function coating.

A hydrophilic matrix tablet consists of mixture of drug, polymer & excipients (filler/diluents as well as other excipients) prepared by hydrophilic polymer in the matrix. Formulators often choose from a range of hydrophilic polymer as stand alone or in combination with different polymers for release rate control. HPMC (20.00%), CMC (12.33%) and magnesium stearate (1.0%). Mixing of powders was performed by geometric dilution method in polythene bag. Then this blend was compressed with multi station - punch tablet machine[36].

Preparation of tablets(procedure for 30 tablets)-

Experimental batch of 25gm each were prepared by direct compression having ibuprofen (66.67%), HPMC (32.33%), and magnesium stearate (1.0%). Mixing of powders was performed by geometric dilution method in polythene bag. Then

Experimental Work

Prepration of Tablets

Experimental batch of 25gm each were prepared by direct compression having ibuprofen (66.67%)

Table1 –Materials required for Batch A

S.No.	Name	Amount In Percentage	Amount Taken(in gm)	Brand or Manufacturer
1.	API(Ibuprofen)	66.67	13.34	Elder Pharmaceutical,dehradun
2.	Hydroxy propyl methyl cellulose	20.00	4.00	Central drug ltd. Bombay- New Delhi
3.	Carboxy methyl Cellulose	12.33	2.46	Central drug house ltd., New Delhi
4.	Magnessium Stearate	1.00	0.20	Central drug ltd. Bombay- New Delhi

Table 2- Materials required for Batch B

S.No.	Name	Amount In Percentage	Amount Taken	Brand or Manufacturer
1.	API(Ibuprofen)	66.67	13.34	Elder Pharmaceutical dehradun
2.	Hydroxy propyl methyl cellulose	32.33	6.466	Central drug ltd. Bombay- New Delhi
3.	Magnessium Stearate	1	0.2	Central drug ltd. Bombay- New Delhi

Table 3 : Weight variation data of Batch A

Weight of 20 tablets = 10.04 , Average weight =0.502gm

Tablet	Individual weight of tablets (gm)	% age weight variation	Tablet	Individual weight of tablets (mg)	%age weight variation
1	0.50	0.398	11	0.49	2.390
2	0.50	0.398	12	0.52	-3.585
3	0.51	-1.593	13	0.50	0.398
4	0.51	-1.593	14	0.52	-3.585
5	0.49	2.390	15	0.49	2.390
6	0.49	2.390	16	0.49	2.390
7	0.50	0.398	17	0.50	0.398
8	0.50	0.398	18	0.52	-3.585
9	0.49	2.390	19	0.51	-1.593
10	0.51	-1.593	20	0.50	0.398

*Limit $\pm$ 5% IP

Table 4 : Weight variation data of Batch B

Weight of 20 tablets = 10.13gm, Average weight = 0.5065gm

Tablets S. no.	Individual weight of tablets (mg)	%age weight variation	Tablets S. no.	Individual weight of tablets (mg)	%age weight variation
1	0.50	1.283	**11**	0.51	-0.691
2	0.52	-2.665	**12**	0.50	1.283
3	0.50	1.283	**13**	0.52	-2.665
4	0.50	1.283	**14**	0.51	-0.691
5	0.49	3.257	**15**	0.49	3.257
6	0.51	-0.691	**16**	0.50	1.283
7	0.50	1.283	**17**	0.49	3.257
8	0.51	-0.691	**18**	0.52	-2.665
9	0.52	-2.665	**19**	0.51	-0.691
10	0.51	-0.691	**20**	0.52	-2.665

*Limit $\pm$ 5% IP

this blend was compressed with multi station - punch tablet machine[36]

Characterisation of Tablets

In - vivo evaluation of the tables is expensive and time consuming. So in - vitro evaluation of tablet is usually done which is rapid and inexpensive. The in - vitro evaluation of the formulated Ibuprofen tablets was done which consists of the following tests [7]

1. Weight variation test

In this test, randomly taken 20 tablets were first weighed together and then individually on the electric balance, dhona220D. Calculate the average weight individually the average weight of the tablets weighing 325 mg and more as according to the IP not more than two of the individual 325mg and more as according to more than two of the individual weights should deviate from the average weight by more than 5%. Observations of the test a given in the table. **Result-**All the tablets of Batch A and Batch B passed the weight variation test.

2. **Friability Test**

The laboratory friability tester is known as the Roche Friabilator[7]. 20 tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution a reweighed tablet sample is placed in friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Tablets that lose less then 0.5 to 1.0% of this weight are generally considered acceptable. Results test of all batches are given in table-4

Table 5 – Friability Test

Batch	Initial wt. of 20 tablet (gm)	Final wt.of 20 tablet (gm)	Friability %age loss	Inference (Result)
A	10.08	9.98	1.00	Pass
B	10.32	13.23	0.879	Pass
C	10.48	10.40	0.760	Pass

*Limit 0.5 to 1.0%

3. Hardness Test

Tablets hardness has been defined as the force required breaking a tablet in diametric compression test. To perform this test, a tablet is placed between the anvils, force is applied to the anvils, and the crushing strength that just causes the tablet break is recorded. Hardness of tablets measured by Monsanto Hardness Tester. Observed data of hardness test of all batches given in table

Table 6: Hardness of Batch A and B-

Tablets	Hardness of Batch A kg/cm^2	Hardness of Batch B kg/cm^2
1	3.4	3.4
2	4.0	3.4
3	4.0	3.6
4	3.8	4.2
5	3.8	3.6

Result- All the Tablets Of Batches A and B show the Hardness within a limit.

Dissolution Test : The process by which drug particle dissolves is termed dissolution. The rate of dissolution directly related to the efficacy of the tablet product, dissolution test is most important parameter of evaluation of tablet. For dissolution study we draw the calibrated curve of different conc. Vs. absorption of pure sample of ibuprofen.

Table 7:Data of standard graph

S.No	Conc. µgm / ml	Abs.
1.	2	0.2125
2.	4	0.3387
3.	6	0.4883
4.	8	0.6053
5.	10	0.8166
6.	12	1.2979

Evaluation of tablets-

In vitro release study was performed using USP apparatus type II[2] Electro Lab at 50 rpm. The dissolution medium used was 900 ml phosphate buffer pH 7.2 for 12 hrs; maintained at 37 ± 0.5°C. The drug release was evaluated by taking sample of 10 ml (which were replaced with fresh medium) at predetermined time intervals and absorbance was measured (λ = 224nm) after filtration and suitable dilution (UV Spectrophotometer Elico).

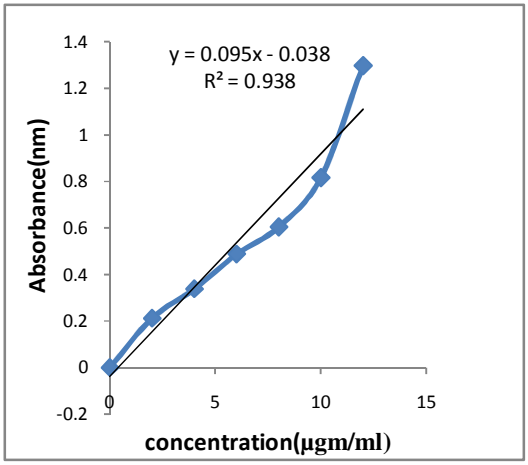

Fig.8: Calibration curve

Result- Dissolution test of Batch A and Batch B was Performed, Batch A which having both polymer HPMC and CMC shown 18.37 % release of drug and Batch B having polymer HPMC shown 15.33 % release of drug in 6 hour.

Conclusion – Two Batches of Ibuprofen sustained release matrix tablet was prepared successfully using HPMC and CMC as polymer to retard release and achieve required dissolution profile. The Combination polymer(HPMC and CMC) of Batch A tablets show Better release rate as compared to Batch B which having HPMC alone.

Table8 - Percentage drug releare from Batch A and Batch B

S.No.	Time(hr)	Abs. of sample A	% Drug release from batch A	Abs. of sample B	% Drug release from batch B
1.	1	0.0045	1.100	0.096	3.840
2.	2	0.0074	1.303	0.260	8.554
3.	3	0.0690	3.071	0.315	10.13
4.	4	0.1263	4.716	0.396	12.45
5.	5	0.4100	12.86	0.440	13.72
6.	6	0.4960	15.33	0.602	18.37

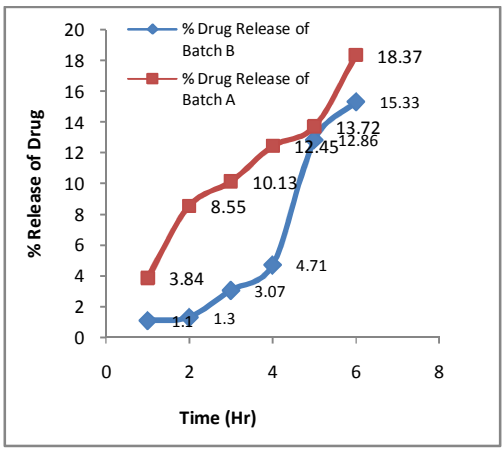

Fig.9- Release rate Curve of both batches.

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