International Journal of Scientific Research and Engineering Development-– Volume 6 Issue 2, Mar-Apr 2023

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

Formulation and Evaluation of Sustained Release Ibuprofen Tablet

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Abstract:

In this study of Ibuprofen it is an (NSAIDs) non steroidal anti- inflammatory drug and used as analgesic & anti-inflammatory drug. It can be also used in the treatment of rheumatoid arthritis, osteoarthritis, and primary dysmenorrheal. Ibuprofen is absorbed rapidly, it has low aqueous solubility so it also lowers the dissolution profile of drug.The main aim of proposed work was to develop Ibuprofen tablets, sustained release dosage form, for the treatment inflammation and pain in the body. Ibuprofen is used to reduce fever and treat pain or inflammation caused by many conditions such as headache, toothache, back pain, arthritis, menstrual cramps, or minor injury. Sustained release formulation is the drug delivery system that designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The tablets were prepared by direct compression method using Hydroxy Propylemethyl Cellulose HPMC(HV),HPMC(LV) and talc.Tablets blends were evaluated for bulk density, tapped density,Carr's Index compressibility index and angle of repose shows satisfactory results.The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 12 hours using paddle method in phosphate buffer (pH7.4) as dissolution media. Formulation F4 shows – of drug release at the end of 12 hours.

Keywords: Ibuprofen, Sustained Release, Dissolution Rate

Keywords — Clinical studies, target discovery and validation, lead optimization, new medication.

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INTRODUCTION

1. **Oral Drug Delivery System**

Oral route of drug delivery is the most preferred route of administration All other routes of drug delivery because of ease of administration,patient compliance and flexible design of dosage form. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take in to account the site specific absorption rates within the gastrointestinal tract (GIT). Therefore there is a need of developing drug delivery system that release the drug at the right time, at the specific site and with the desired rate.[1,2]

2. **Sustained Release Drug Delivery System**
Sustained release dosage form that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.Sustained release tablets are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times a day to attain the same required drug to produce the effect. the sustained release dosage form is to provide proper amount of drug at regular time interval and at right site of action to maintain therapeutic range of drug in blood plasma.The concept of sustained release dosage products was previously used to describe various types of oral sustained release dosage forms, including delayed release, extended release, controlled release, prolonged action, repeat action targeted release dosage forms.

Delayed release dosage form: It is a dosage form which indicates that the drug is not being released immediately following administration but at a latertime, e.g. enteric coated tablets.

Extended-release dosage form: It is a dosage forms release drug slowly, so that plasma concentration is maintained at a therapeutic level for a period of time

Prolonged release dosage form: It is a dosage form which indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form.

Controlled release dosage form: It is a dosage form that maintains constant drug levels in blood or tissue. [3,6]

3. **Advantages of Sustained Release Drug Delivery System**
   I. Reduction in dosing frequency.
   II. Reduced fluctuation in circulating drug levels.
   III. Increased patient convenience and compliance.
   IV. Avoidance of night time dosing.
   V. More uniform effect. [7,8]
4. **Disadvantages of Sustained Release Drug Delivery System**
   I. The physician has less flexibility in adjusting dosage regimens.
   II. Poor in vitro-in vivo correlation.
   III. Chances of dose dumping and burst effect.
   IV. Delayed onset of action , hence not useful in acute condition.
   V. Higher cost of formulation.[9,10]

5. **Rationale of Sustained Release Drug Delivery System**
   I. To extend the duration of action of the drug.
   II. To Reduce the frequency of dosing.
   III. To minimize the fluctuation in plasma level.
   IV. Less adverse effects.[11]

6. **Drug Properties Relevant to Sustained Release Formulation**
The formulation of sustained release drug delivery systems, consider the some criteria such as the route of administration, type of drug delivery system, whatdisease to be treated, the patient, the duration of treatment and the characteristic of the drug those above mentioned factor should be considered. The pharmaceutical interest to research scientist for designing of the delivery system the following properties could be considered in the development of

dosage form. These properties can be classified as follows.

A) Physicochemical properties

B) Biological properties

The properties having the greater importance in the design of the drug in the delivery system and in the body. But there is no distinction between these two categories because the biological properties of a drug as like a function of its physicochemical properties. By definition, physicochemical properties of drug they can be determined from in vitro study and biological properties will be those that result from Pharmacokinetic studies such as absorption, distribution, metabolism and excretion of a drug and those resulting from pharmacological experimental study

A. **Physicochemical Factors Influencing Oral Sustained-Release Dosage Form Design:**

a) **Dose size:** For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5- 1.0g 5 is considered maximal for a conventional dosage form. This also holds for sustained release dosage form.

b) **Ionization, pka and aqueous solubility:**Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment.

c) **Partition Coefficient:** When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body.

d) **Drug Stability:**Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases.

e) **Protein binding:**Its properties the drugs are binding to blood protein. The drug-Protein complex it can act as a depot for drug molecule and to release a drug for prolonged period and leads to exhibit a highly binding to plasma.

B. **Biological factors influencing oral sustained-release dosage form desige**

a) **Biological half life:** The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated.

b) **Absorption:** Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower 6 than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours.

c) **Metabolism:** Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slowerreleasing dosage form.[12]

7. **Design and fabrication of oral systems**The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms.The following techniques are employed in the design and fabrication of oral sustained release dosage forms.

I. **Dissolution controlled release Matrix dissolution control**

II. Diffusion controlled release Reservoir devices Matrix devices

III. Diffusion and dissolution controlled systems.

IV. Ion-exchange resins

V. pH - independent formulations

VI. Osmotically controlled release

VII. Altered density formulations. [13,14,15]

8. Methods used in tablet manufacturing

a) Wet granulation
b) Dry granulation
c) Direct compression

C) Direct compression:

Size reduction of active component and inactive component, mixing of milled ingredients, tablet compression.

2 Advantages of Direct Compression Method

1. The exposing of active component to moisture and thermal can be prevented.These methods the cost of preparation can be minimized and reduce the labor cost.
2. Tablet manufactured by this process very easy to disintegrating molecule from the dosage form.
3. The equipment like granulators and dryers and solvent are not needed in manufacturing of tablets by this method.

3Disadvantages of Direct Compression Method

1. The uniformity of color is difficult to achieve in manufacturing of tablets.
2. In this process cost of materials is a great vertical extent.
3. In this method produce dust and air pollute during manufacturing process.[16,17]

4 Plan of Work:

A) Formulation of Sustained Release Tablet of Ibuprofen
1 : Drug and Excipients Profile
2 : Material and Equipments

B) Evaluation of Sustained Release Tablet of Ibuprofen
1: Organoleptic properties
2 :Hardness
3 :Percent friability
4 :Weight variation test
5 :Dissolution test

C) Conclusion

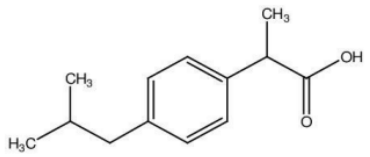
D) References

5 Drug and Excipients Profile

5.1. Drug Profile

5.1.1.Ibuprofen: Chemically,Ibuprofen is described as 2-(4- isobutylphenyl)propionic acid and is a nonsteroidal compound, which exhibits high levels of anti-inflammatory, analgesic and antipyretic activities necessary the effective treatment of rheumatoid arthritis and osteoarthritis. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID), which relieves pain and swelling (inflammation). It is used to treat headaches, muscle aches, backaches, dental pain, menstrual cramps, arthritis, or athletic injuries. This medication is also used to reduce fever and to relieve minor aches and pains due to the common cold or flu. This drug works by blocking the enzyme in your body that makes prostaglandins. Decreasing prostaglandins helps to reduce pain, swelling, and fever

Structure:



Ibuprofen

(IUPAC) name (RS)-2-(4-(2-methylpropyl) phenyl) propionic acid

Table :Physico – Chemical Properties of Ibuprofen

Discription	White or almost white colored crystalline powder
Chemical name	2-(4-isobutylphenyl) propionic acid
Molecular formula	C13H18O2
Molecular weight	206.29 g/mol
Melting point	75-77 °c
Functional category	Ibuprofen is used for the treatment of mild to moderate pain inflammation and fever caused by many and diverse diseases
Storage condition	Ibuprofen should be stored at room temperature , between 15-30°c

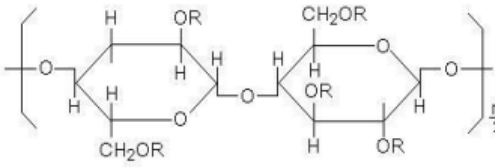
5.2. Polymers Profile:

5.2.1. Hydroxy Propyl Methyl Cellulose

Synonyms : HPMC,Methocel, Hydroxy propyl methyl cellulose.

Molecular weight: 10,000-15,000

Structure



Description : slightly off-white to being powder in appearance and may be formed into granules.

Color : white to yellowish white

Odour : odorless

Taste : tasteless

Texture : powder [20]

6. **Material and Equipment**

6.1 Materials

Name of Ingredients	**Name of Supplier**
Ibuprofen	Purches from pure chem., baramati
HPMC (LV)	LobaCheme
HPMC (HV)	LobaCheme
Talc	Cosmo Chem

6.2 Equipment's Used

List of equipments with model

Equipment's Names

1. Electronic balance
2. Bulk density apparatus
3. Hot air oven
4. One punch tablet compression machine
5. Friability apparatus
6. Hardness tester
7. UV spectrophotometer

7. Experimental Work

7.1 Formulation of Ibuprofen Sustained Release Tablet

Procedure:

1 : Weighed all the ingredients accurately separately by using electronic balance.

2: Mix all the ingredients and sieve by using sieve repeat these process 4 times .

3: Then check all the evaluation parameters.

4: weigh all the ingredients as bacth wise.

5: For preparation of ibuprofen we use 22 factorial design.

Table 7.1: Composition of Ibuprofen tablet

Ingredients (mg)	F1	F2	F3	F4
Ibuprofen drug	**150**	**150**	**150**	**150**
HPMC (LV)	**25** (-)	**100** (+)	**25** (-)	**100** (+)
HPMC (HV)	**25** (-)	**25** (-)	**100** (+)	**100** (+)
Diluent	**150**	**75**	**75**	**00**
MCC	**25**	**25**	**25**	**25**
Total	**375**	**375**	**375**	**375**

7.2 Evaluation of powder–

1. **Angle of repose:** It is the maximum angel between the surface of a pile of powder and horizontal plane.

   tanθ = h/r

   Where, h and r are the height and radius of the granules cone respectively. The rougher and more irregular the surface of the particles ,the higher will be angel of repose,lower the value indicate better flow characteristics.

Table : The acceptance criteria for angle of repose

Sr.no	Flowability	Angle of repose (degree)
1	Excellent	<20
2	Good	20-30
3	Passable	30-37
4	Poor	37-45
5	Very poor	>45

1. **Bulk density:** The bulk density value includes the volume of all of the pores within the powder sample.
   Bulk Density = Weight / Bulk Volume.
2. **Tapped Density:** The tapped is an increased bulk density attained after mechanically tapping a container containing the powder sample.
   Tapped Density =Total weight of powder/ Tapped volume.
3. **Hausner ratio:** Hausner ratio is the ratio between tapped density and bulk density. Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules.
   Hauser's ratio = Tapped density/Bulk density Acceptance criteria for Hauser's ratio

5 :Carr's compressibility index: It is a simple index that can be determinedon small quantities of powder. By decreasing the bulk and tapped density good flow properties can be obtained.

Carr's compressibility index (%) = [(Tapped density-Bulk density)/ Tapped density] ×100

Carr'sindex(%)	Flowability
5=15	Excellent
12=16	Good
18=21	Fairly accepted
23=35	Poor
33=38	Very poor
40	Very very poor

The acceptance criteria for the Carr's index

7.3 Quality test for tablet

A : Non official test B : Official test
1 : General appearance 1 : weight variation
2 : Hardness test 2 : content uniformity
3 : Friability test 3 : Dissolution test

A. General appearance : It involves the measurements of size ,shape , Color,odor and taste

B. Hardness test : Hardness test is also known as crushing strength test.Tablet require a certain amount of strength or hardness to with stand mechanical shock of handling in manufacturer in packaging and shipping..The official range of hardness stated in and USP is not less than 4.00kg of pressure

C. Friability test : Friability is defined as the percentage of weight loss of powder from the surface of the tablets due to mechanical action and the test is performed to measure the weight loss during transportation. Friability (%) =W1 – W2/ W1 X 100

Where, W1 = Weight of Tablets (Initial / Before Tumbling) & W2 = Weight of Tablets (After Tumbling or friability)

Limit : Friability (%) = Not More Than 1.0 %

1.**Weight variation** :

The test for uniformity of weight is performed by weighing individually 20 tablets randomly selected from a tablet batch and determining their individual weights. The individual weights are compared with the average weight.The sample complies with USP standard if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table: Specifications of %Weight variation allowed in tablets as per IP.

Hauser's ratio	Types of Flow
<1.25	Good flow
>1.50	Poor flow
1.25=1.50	Glidant addition required

As per IP/BP	Average Mass Limit	As per USP
Tablet weight 80 mg or less	±10 %	Tablet weight 130 mg or less
More than 80 mg or Less than 250mg	± 7.5%	130mg to 324 mg
250 mg or more	± 5 %	More than 324 mg

8. Result and Discussion

8.1 Evaluation of Sustained Release Ibuprofen Tablet.

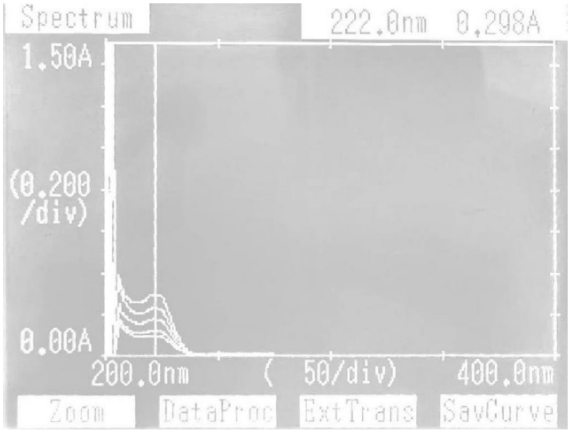
8.1.1 λmax Determination in Phosphate buffer pH 7.4: The absorption maximum for Ibuprofen was found to be 222 nm.

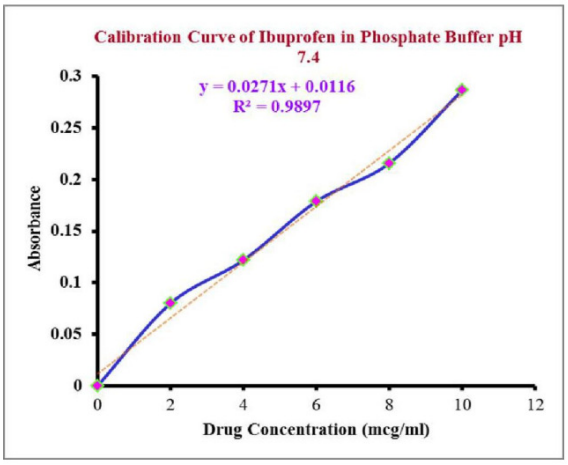
8.1. 2 Preparation of standard curve of Ibuprofen

Sr .no	Concentration (µg/ml)	Absorbance
0	0	0.00
1	2	0.08
2	4	0.122
3	6	0.179
4	8	0.216
5	10	0.287

8.2. By using in Phosphate buffer pH 7.4: UV absorption spectrum of Ibuprofen in Phosphate buffer pH 7.4 shows λmax at 222 nm. Absorbance obtained from various concentrations of Ibuprofen Phosphate buffer pH 7.4 is are given in table 8.2 The graph of absorbance vs concentration for Ibuprofen was found to be linear in the concentration range of 0 – 10µg/ml.

Table 8.2 Concentration and absorbance for Ibuprofen in Phosphate buffer pH7.4





8.3 Flow properties of Powders

Formulation code	Angle of repose	Bulk density (g/cm2)	Tapped density (g/cm2)	Carr's Index %	Hauser's Ratio %
F1	34.28°	0.40	0.46	13	1.15
F2	25.70°	0.41	0.52	21.1	1.25
F3	24.17°	0.39	0.49	20	1.25
F3	32°	0.43	0.52	17	1.20

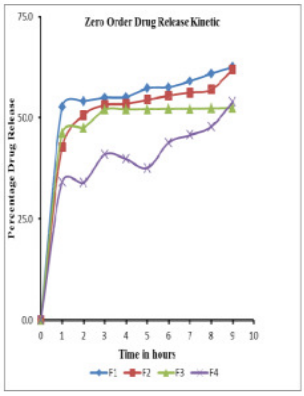
8.4 .Evaluation of sustained release tablets:

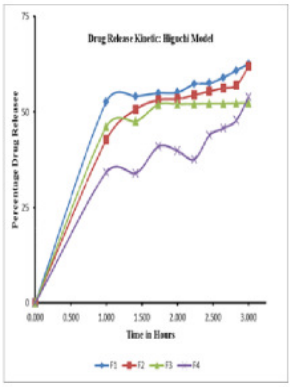
8.4.1 **Appearance:** The tablets were observed as white colored.

Formulation code	Hardness (g/cm2)	Friability %	Weight Variation %
F1	3-4	1.80	1.36
F2	3-4	1.78	1.36
F3	3-4	1.84	1.87
F4	3-4	1.82	2.70

8.4.2 In-Vitro Dissolution Studies

Sr.No	Time (hrs.)	Drug Release Profile			
		F1	F2	F3	F4
1	0	0.00	0.00	0.00	0.00
2	1	52.70	42.74	46.16	34.17
3	2	54.07	50.65	47.52	33.91
4	3	54.96	53.17	52.01	40.95
5	4	55.13	53.44	52.07	39.82
6	5	57.29	54.43	52.14	37.59
7	6	57.55	55.46	52.21	43.87
8	7	59.05	56.26	52.24	45.73
9	8	60.91	56.99	52.31	47.82
10	9	62.57	61.90	52.44	53.87
R^2		**0.4305**	**0.5136**	**0.369**	**0.6554**
Zero Order		**y=3.972x+33.549**	**y=4.1988x+29.609**	**y=3.2679x+31.04**	**y=3.912x+20.155**
R^2		**0.6918**	**0.775**	**0.6463**	**0.8536**
Higuchi Model		**y=16.451x+19.662**	**y=16.852x+15.969**	**y=14.131x18.628**	**y=14.599x+9.5892**





Conclusion: Ibuprofen is poorly water soluble drug Lower by oral Sustained of Ibuprofen by direct compression method the dissolution of Ibuprofen Lowered. The result showed that the dissolution rate of drug in oral Sustained tablet was lowered than pure drug. It means oral Sustained

tablet form of Ibuprofen strongly Decrease the dissolution of Ibuprofen Direct compression method can be used, because it is an easier, simplified and the dissolution of Ibuprofen Direct compression method can be used, because it is an easier economical method of manufacturing of tablets. After in vitro dissolution study the R2 value of F4 in Zero order relkease kinetic is 0.6554 and F4 in Higuchi model is 0.8536 respectively. So that F4 follows Zero order kinetic and it release drug by sustained release.

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