DEVELOPMENT AND CHARACTERIZATION OF FAT-WAX MATRIX TABLETS OF FLURBIPROFEN BY MELT GRANULATION TECHNIQUE USING NATURAL AND SYNTHETIC EXTENDERS

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Abstract

The Fat wax matrix tablets of Flubriprofen were prepared by melt granulation technique using various compositions like oleic acid and carnauba wax, bees wax, Magnesium sterate, Talc, micro crystalline cellulose, with different concentration. Total number of nine formulations was prepared and evaluated. The direct correlation between, dissolution profile for the optimized formulation F3 containing oleic acid and carnauba wax as a disintegrating agent. After evaluation it has been noted that Batch F3 containing oleic acid has shown good results in powder characteristics, post formulation evaluation and hence it was considered as an optimized formulation. Disintegration of batch F5 was less than all other batch. Hardness and Friability of batch F3 were also good. Stability study indicated that there was no change after one month.

Keywords: Flubriprofen, Melt granulation technique, Starch, Talc

1. Introduction

Approaches to overcome these limitations

Development of new, better and safer drugswith long half-life and large therapeutic indicesEffective and safer use of existing drugsthrough concepts and techniques of controlled andtargeted drug delivery systems.The first approach has many disadvantages,however second approach can be used widely [4-5]. An ideal controlled drug delivery systemis thatwhich delivers the drug at a specific rate locally or systemically for a specified period of time withminimum fluctuation in plasma drugconcentration,reduced toxicity and maximum efficiency[6].

Oral Drug Delivery Systems

The term “Drug Delivery” covers a very extensive range of techniques used to deliver therapeutic agents into the human body. Drugs are administered with a main aim of curing patient ailments. Drugs are never administered in their pure form but are converted in a suitable formulation so that its onset and intensity of action as well as total duration of action

can be checked. Among the various routes of drug delivery oral route is most widely used route of drug delivery. But conventional dosage form offers few limitations which could be resolved by modifying the existing dosage form [1-2].

Biopharmaceutical aspects of route of administration:

Oral **a**nd parental (I'm.) routes followed by transdermal are most popular. Routes of minor importance in sustained drug delivery are buccal/sublingual, nasal, rectal, ocular and pulmonary [7,8]. A detailed knowledge of ADME characteristics of drug is essential in the design of sustained release product. An optimum range of given pharmacokinetic parameter of a drugis necessary beyond which controlled/sustained delivery is difficult.

Formulation Strategies for Oral Sustained Release System

1. Diffusion Sustained Release
2. Dissolution Sustained Release
3. pH Dependent System
4. Altered Density System Osmotic Pump System
5. Ion Exchange System

Types of dissolution sustained system:

- Matrix/Monolith Dissolution System.
- Encapsulation/Coating/Reservoir System.

Types of altered density system:

- High Density System
- Low Density System
- Muco Adhesive System

Types of diffusion sustained system:

- Swellable matrix
- Reservoir/Laminate matrix

Ion exchange resins:

Based upon the principle that GIT has a relatively constant level of ions, this type of system has developed for controlling the rate of delivery of ionizable or ionic drugs. Such a system can be prepared by incubatingthe drug resin solution or by passing the drug solution through a column containing exchange resin. A cationic drug is complexed with a resincontaining SO3- group and for anionic drug resincontaining N(CH3)3 group is used. In the GI Hydronium and chloride ions diffuses into the sustained release tablet and interact with drugresincomplex to trigger the release of drug.[14].

Coating dissolution system:

In this type of system the drug particles are coated with polymers like cellulose, polymethaacrylate, PEGs etc. The resulting pellets are compressed as tablets. The dissolution rate of the coat depends upon thickness and solubility of coat. [12,13]

Porous matrix-controlled system:

In this this type of system the rate controlling element is a water swellable material (hydrophilic polymers and gums) like alginates, xanthan gum, locustbean gum, HPMC etc. or a non swellable water insoluble polymer like ethyl cellulose.

Porous membrane-controlled system:

In thesetype of system the rate controlling element is a water insoluble non swellable polymer like ethylcellulose, polymethaacrylate etc. which controls the drug release through the micro pores present in their membrane or matrix structure [9,10,11].

Soluble matrix system:

These systems are also known as monoliths as the drug is homogenously dispersed in a rate controlling medium. Waxes like bee wax, carnauba wax etc. are used for controlling the dissolution rate. The rate of dissolution is controlled by either of following mechanisms:

- Altering the rate of fluid penetration into tablet by altering the porosity of tablet.
- Decreasing the wettability of tablet.
- Slow dissolution rate of polymer.

2. Materials And Methods

Materials:

Flurbiprofen was obtained as a gift sample from Aspire LiveScience's Ltd Mumbai. Polymers obtained from India mart. Bees wax and carnauba wax. Excipients obtained from trade India chemicals, Hyderabad. Magnesium sterate, Talc, Microcrystalline cellulose, Starch, Talc, Potassium dihydrogen orthophosphate, sodium hydroxide and other chemicals are of analytical grades.

Methods:

Formulation of Fat Wax Matrix Tablets of Flubriprofen

Calculate and weigh accordingly all the ingredients for 50 tablets from given formula. First melt Bees wax, carnaubas wax and oleic acid in porcupinefish. This melt mixture is then transfer through 10# sieve to get granules. They are mixed with rest half quantity of talc. These granules are then again passed through 40# sieve and mixed with talc. Tablets are prepared using 9m punch size. The method is called melt granulation technique. The mass was passed through a sieve no.16 to obtain wet granules. The wet granules were dried at 50ºC for 30 minutes. Dried granules were passed through sieve no.21 to remove the aggregates. These granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets on a rotary multi-station tableting machine with required hardness using 9 mm round and flat punches.

Table-1. Formulation of Flurbiprofen Tablets

S.no	**Ingredients**	FLB-1	FLB-2	**F**LB-**3**	FLB-4	FLB-5	FLB-6	FLB-7	FLB-8	FLB-9
1.	Flurbiprofen	50	50	**50**	50	50	50	50	50	50
2.	carnauba Wax	50	--	**--**	100	--	**--**	75	--	--
3.	Oleic acid	--	75	**--**	--	50	**--**	--	100	--
4.	Bees Wax	--	--	**100**	--	--	75	--	--	50
5.	Microcrystalline cellulose	50	50	**30**	30	50	50	50	30	50
6.	Starch	40	15	**10**	10	40	15	15	10	40
7.	Talc	5	5	**5**	5	5	5	5	5	5
8.	Magnesium stearate	5	5	**5**	5	5	**5**	5	5	5
Total Weight in mg		200	200	**200**	200	200	200	200	200	200

Experimental work

Mobile phase:

Prepare a filtered and degassed mixture of pH 3.2 Citrate buffer and acetonitrile (1685:315). Make adjustments if necessary (see System Suitability under Chromatography 621).

Standard stock preparation:

Dissolve an accurately weighed quantity of USP Flubriprofen Mobile phase, and dilute with Mobile phase to obtain a solution having a known concentration of about 0.5 mg per ml.

Standard preparation:

Transfer 10.0 mL of Standard stock preparation to a 50-mL volumetric flask, and dilute with Mobile phase to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with Mobile phase to volume and mix.

Identification test-Preparation of citrate buffer pH 3.2.

Dissolve 12.0 g of sodium citrate dihydrate and 28.5 g of anhydrous citric acid in 1.95 L of water. Adjust with anhydrous citric acid or sodium citrate to a pH of 3.2 ± 0.1. Dilute with water to 2.0 L, and mix.

Assay stock preparation:

Transfer about 100 mg of Flubriprofen, accurately weighed, to a 200-mL volumetric flask; dissolve in and dilute with Mobile phase to volume; and mix.

Assay preparation:

Transfer 10.0 mL of Assay stock preparation to a 50-mL volumetric flask, dilute with Mobile phase tovolume, and mix. Transfer l0.0 mL of this solution to a l00-mL volumetric flask, dilute with Mobile phase tovolume, and mix.

Chromatographic system:

The liquid chromatography is equipped with a 254-nm detector and a 4.6-mm × 25-cm column thatcontains packing L7. The column temperature is maintained at about 30. The flow rate is about 1.0 mL perminute. Chromatograph the Mobile phase, and record the peak responses as directed for Procedure: ensurethat there are no significant interfering peaks. Chromatograph the Standard preparation, and record thepeak responses as directed for Procedure: the column efficiency is not less than 12,000 theoretical platesthe tailing factor is not less than 0.9 and not more than 1.3; the relative standard deviation for replicate injections is not more than 0.9%.

Procedure:

Separately inject equal volumes (about 20 μL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms for about 45 minutes, and measure the peak responses.Calculate the quantity, in mg, of C19H25N5O4·HCl in the portion of Flubriprofentaken by the formula: 10,000C(rU/rS)in which C is the concentration, in mg/mL, of USP Flubriprofenin the Standard preparation;andrU and rS are the peak responses obtained from the Assay preparation and the Standard preparation,respectively [11] .

UV-Visible Spectrophotometric method:

Calibration curve of Flurbiprofen was made in 0.1N HCl and Phosphate buffer of pH 6.8 by preparing a serial of dilutions of Flurbiprofen with different concentrations (1, 2, 4, 8, 10, 15, 20 μg/ml) from stock solution containing 40mg/100ml Flurbiprofen. The absorbance was then measured at the λmax of the drug. The measured absorbance was plotted against the respective concentrations. [12].

Preformulation studies:

Angle of Repose:

Angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the equation θ = Tan-1 h/r.[13]

Density of powder:

A powder blend from each formulation was introduced in to a 10 ml glass measuring cylinder. The initial volume and weight was noted. The cylinder was tapped 50 times on to a hard surface from a height of 2.5 cm at an interval of one second. Tapped volume was noted. Based upon the data obtained Untapped Bulk Density and Tapped Bulk Density were calculated.[14]

Compressibility Index and Hausner's Ratio:

Compressibility Index and Hausner Ratio of powder blend was determined by using Tapped bulk density and untapped bulk density.

Post compression studies:

The tablets were tested for its Drug content estimation, wetting time, In vitro dispersion time, physical appearance, thickness and diameter using Verniercallipers; weight variation using Digital weighing balance Sartorius- GE612; Hardness using Pfizer hardness tester; Friability using Roche friabilator. In-vitro disintegration and dissolution time were also determined.

Wetting time:

A piece of tissue paper doubly folded was placed in a Petri plate having an internal diameter of 8.5 cm containing 6ml of SSS pH 7.4. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.[15]

Physical appearance:

The physical appearance was determined by visual inspection

Thickness and diameter

The thickness and diameter was measured by vernier calipers and recorded.

Weight variation:

As per IP guidelines to perform test for uniformity of weight 20 tablets from each batch were selected randomly and their average weights were calculated using a digital weighing balance (EssaeTeraoka ltd). Percentage weight difference was calculated and checked with IP specifications.

Hardness

A diametric compression test was performed according to European Pharmacopeial method 2.9.8 using Monsanto Hardness Tester. According to standard literature in case of sublingual tablet hardness of 2 kg/cm2 was acceptable [15].

Friability:

The friability test was performed according to the IP guidelines. Since the tablet weight **(**130 mg) was always less than 650 mg, a random sample of whole tablets corresponding to 6.5 g was dedusted, accurately weighed, and placed in the drum of a Roche Friability tester (Mfg by Koshiash Industries). Drum was rotated 100times and tablets were removed, dedusted, and accurately weighed. A maximum weight loss of not more than 1.0% was considered acceptable [14].

Drug content

Ten tablets were collected and grounded using a glass mortar and pestle to obtain a fine powder. Accurately weighed powdered sample equivalent to 50 mg of drug was transferred to 50ml volumetric flask. About 15ml methanol and 2 ml of 0.1M sodium hydroxide solution was added to added to extract and dissolve the drug. The mixture was sonicated for 15 min to ensure complete extraction and the final volume was made up to the mark with methanol. From this 1ml was taken in 100 ml volumetric flask and made up to the mark with pH 7.4 phosphate buffer. The absorbance of this solution was measured using phosphate buffer as blank. The samples were analyzed for Flurbiprofen using double beam spectrophotometer) at 247 nm. The drug content was obtained from calibration graph[12].

Dissolution test:

In-vitro dissolution studies of tablets were carried out using US apparatus II paddle method. Tablets were placed in 900 ml of 0.1NHCL at 37+0.5°C stirred at 100 rpm. Samples of 1 ml were withdrawn at different time intervals. An equal volume of fresh dissolution medium was immediately replaced. The samples werefiltered and analyzed spectrophotometrically at 247 nm.[12]

3. Results And Discussion

Table.1Standard calibration curve

S.No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	2	0.022
3	4	0.043
4	6	0.057
5	8	0.084
6	10	0.113
7	12	0.123

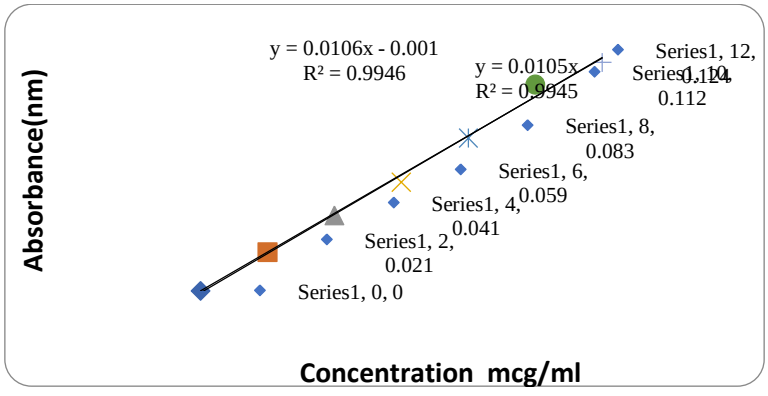

Figure.7. Standard curve of Flubriprofen

Absorbance on y axis and concentration on x-axis

Pre compression evaluation studies:

Table.2 Evaluation of tablet blend for formulations (F1-F9)

Formulation	Bulk Density	Tappe	Hausner's	Compressibility	Angle of

Codes	(g/cc)	Density	ratio	Index (%)	repose
FLB1	0.464	0.567	1.22	17.1	23.45
FLB2	0.412	0.543	1.29	18.4	24.35
FLB3	**0.451**	**0.578**	**1.23**	**19.1**	**31.34**
FLB4	0.432	0.541	1.27	12.1	22.12
FLB5	0.442	0.532	1.16	13.8	29.11
FLB6	0.321	0.549	1.31	12.5	28.11
FLB7	0.439	0.519	1.28	11.9	29.12
FLB8	0.412	0.512	1.21	12.3	20.19
FLB9	0.421	0.412	1.12	14.5	21.67

Table.3Post compression evaluation of Flubriprofen formulations (F1 – F9)

Formulation Batches	Weight variation (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm2)	Drug Content (%)
FLB 1	274±0.59	3.9±0.03	0.25	3.0±0.17	97.1±0.17
FLB 2	271±0.43	4.1±0.02	0.26	4.1±0.14	92±0.14
FLB **3**	**275±0.17**	**3.9±0.07**	**0.26**	**3.1±0.18**	**98±0.17**
FLB 4	275±0.32	3.2±0.06	0.32	4.3±0.16	90±0.16
FLB 5	275±0.59	3.7±0.02	0.23	3.8±0.21	93±0.12
FLB 6	275±0.49	4.6±0.02	0.21	4.1±0.12	93±0.13
FLB 7	275±0.69	4.1±0.05	0.24	2.9±0.15	92±0.16
FLB 8	275±0.29	2.9±0.02	0.36	4.8±0.17	90±0.12
FLB 9	275±0.39	4.0±0.02	0.28	3.2±0.16	89±0.15

Table.4Cumulative % drug release for formulations (F1 – F9)

Time in Hrs	F1	F2	**F3**	F4	F5	F6	F7	F8	F9
0	0	0	**0**	0	0	0	0	0	0
1	25.12	39.90	**45.12**	55.16	54.5	43.13	55.19	50.19	34.19
2	34.12	45.32	**56.87**	64.94	62.90	55.15	65.17	64.92	55.17
3	54.20	55.67	**67.98**	74.65	71.64	65.17	72.18	78.19	79.13
4	70.34	68.19	**73.90**	84.12	81.12	70.19	79.91	89.18	84.19
5	74.70	76.12	**89.19**	90.16	87.15	85.19	86.54	89.90	89.76
6	85.16	81.21	**93.83**	89.43	90.16	89.15	90.19	90.10	91.13

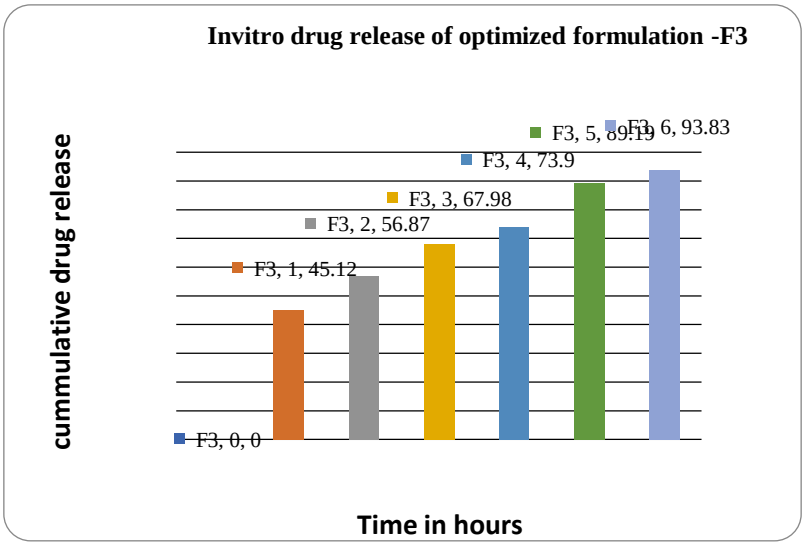

Figure-8Bar graph of Invitro drug release Flubriprofen–F3

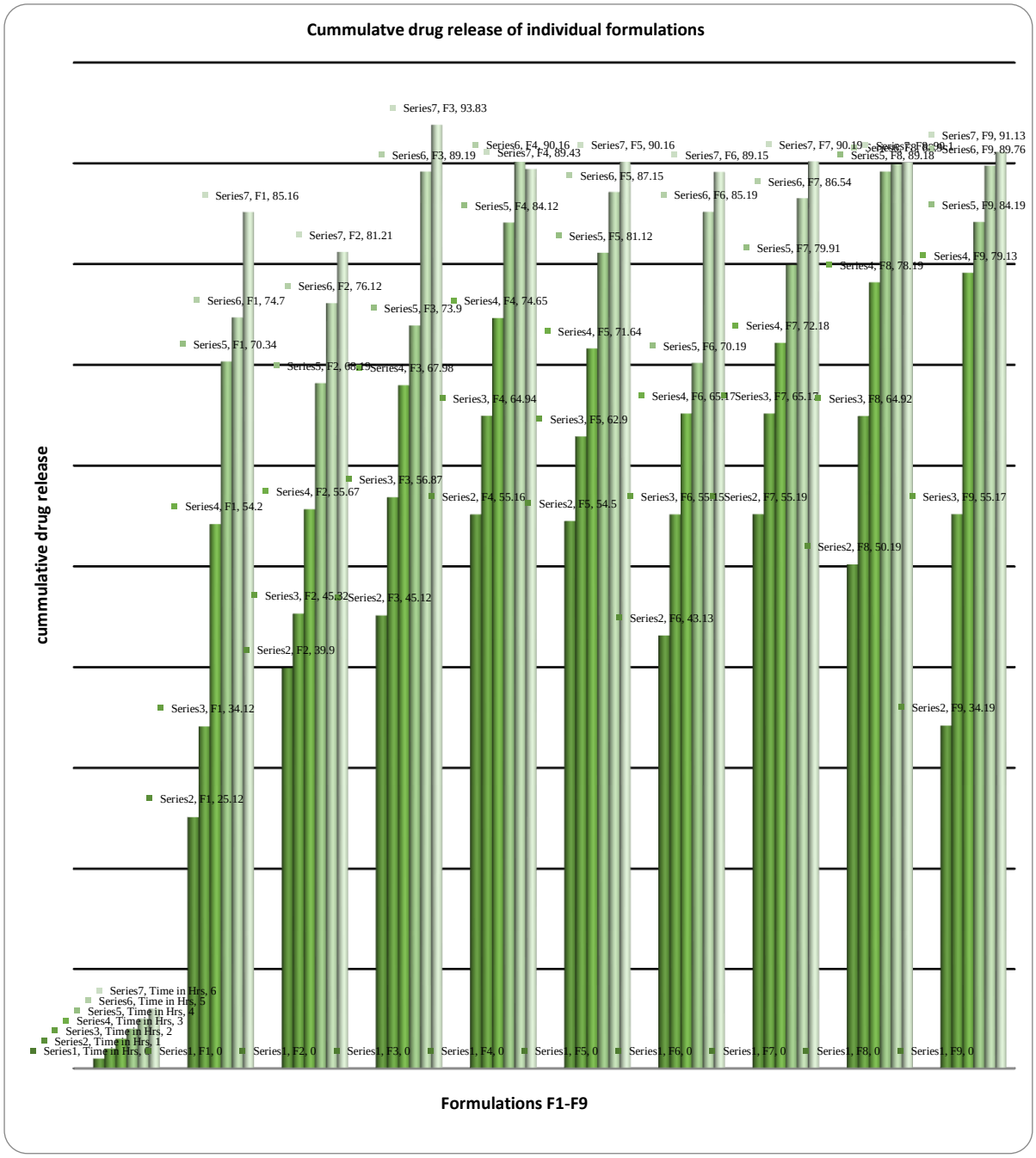

Figure-9Bar graph of cumulative drug release of Flubriprofen F1-F9

4. Discussion

The different batches of Flurbiprofen fat wax matrix tablets were prepared by melt granulation technique using various pharmaceutical excipients like carnauba wax and bees wax, Magnesium sterate, Talc, micro crystalline cellulose, oleic acid, and starch. The total number of nine formulations with different concentration of oleic acid and carnauba wax and bees wax were prepared and pre-formulation followed by post-formulation studies were done and the results were plotted. the results are shown in table 2, 3 and 4. Magnesium sterate act as a diluents and oleic acid,carnauba wax and bees wax used as disintegrating agents at a ratio of 1-1.5-2.0. The formulation of batch **F3** was considered as an optimized formulation

as it has show good drug release characteristic 93.83 % with MCC 30% and starch 10%. When compared to other formulation batches. The Hardness, thickness and Friability of batch optimized **F3** was found to be good. Stability study and in batch **F3** as per ICH Guidelines. Stability study indicated that there was no change observed after one month.

5. Summary and Conclusion

The concept of tablets containing Flubriprofenoffers a suitable and practical approach in serving the desired objective of management of pain. The excipients used in the formulation were inexpensive and are easily available. Most of the excipients used in formulation are water-soluble and hence have a better patient acceptability. The present work of formulating a fat wax matrix tablet containingflubriprofenwas successful in terms of reducing manufacturing difficulties, cost and providing a betterpatient compliance with effective medication. It has been observed from the above study that excipients like oleic acid and carnauba wax Excipients obtained from trade India chemicals, Hyderabad. Magnesiumsterate, Talc, microcrystalline cellulose, starch etc. Were ideal excipients and effective for formulating fat wax matrix tablets of Flubriprofen prepared by melt granulation technique. Matrix tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within prolonged period may be achieved. The batch F3 was considered to be the best among all other batches since it exhibited a good dissolution profile, when performed individual and combination with better uniformity of drug content.

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