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Research

Formulation development and *in vitro* characterization of flurbiprofen sustained release matrix tablets

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Abstract

In the present work, an attempt has been made to develop Sustained release tablets of Flurbiprofen by selecting natural polymers Tragacanth, Acacia gum, and Xanthan gum as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F2 formulation showed maximum % drug release i.e., 95.19% in 12 hours hence it is considered as optimized formulation F2 which contains Tragacanth (100 mg). Optimized formulation F2 was followed Higuchi release kinetics mechanism.

Keywords: Flurbiprofen, Tragacanth, Acacia gum, Xanthan gum and sustained release tablets.

INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. Sustained-release medications are usually labeled with “SR” at the end of their name. These medications prolong the medication's release from a tablet or capsule so that you'll get the medication's benefits over a longer period of time. Sustained-release medications should not be used alone to adjust or titrate a patient's uncontrolled pain. Using them for titration unduly prolongs the process to bring the pain under control. However, once the pain is controlled, changing to a sustained-release product may enhance the patient's quality of life and improve compliance and adherence due to the decreased frequency of dosing.

Advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into
Better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The product so formulated are designated as sustained action, sustained release, delayed action, prolonged action, depot, respiratory, retarded release and timed release medication. Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s. Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e. the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/ or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will requireless frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administered every twelve hours. In another instance, it may be desirable to decrease the absorption rate in order to obtain a more acceptable clinical response (Girish K Jani, 2009).

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because of the fact that there is more feasibility in dosage form design for oral route than for parenteral or any other route. The design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance. Among these are the types of delivery systems, the disease being treated, the patient and the length of therapy and the properties of the drug.

1.1. DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS[10-12]:

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

Table 1: Parameter for drug selection

Parameter	Preferred value
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
Pka	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.

Table 2: Pharmacokinetic parameter for drug selection

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent

Elimination rate constant	Required for design
Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Advantages of Sustained release drug delivery system over the conventional dosage form[13]:

- Reduced dosing frequency
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate. (Figure1) shows the relation between plasma concentration verses time.

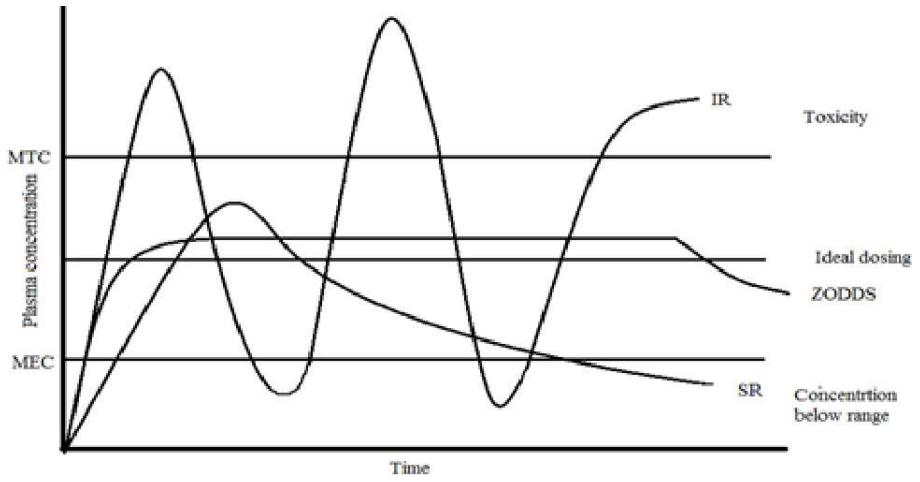

Fig 1: Ideal Plasma Concentration Curves For Immediate Release, Zero Order Release,

Sustained Release Drug Delivery System

Factors affecting the formulation of oral sustained release drug delivery system[14,15]

Physicochemical factors

Aqueous Solubility

Most of the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption.

Partition coefficient (P (o/w)

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes though biological membrane, if partition coefficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition coefficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane .

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0% .

Drug stability

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation .

Molecular size and diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteinsand peptides.

MATERIALS

Flurbiprofen-Procured From Amar Healthcare (India). Provided by SURA LABS, Dilsukhnagar, Hyderabad. Tragacanth-Loba Chemie Pvt. Ltd Mumbai, India,Acacia gum-Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum-Aravind Remedies (AR), Chennai, India, PVP-K 30-Unify chemicals, Jothi Aromas and, DK-Enterprises, India, Aerosil-S.D. Fine Chemicals. India, Magnesium Stearate-Merck Specialities Pvt Ltd, Mumbai, India, Lactose-S.D. Fine Chemicals, India

METHODOLOGY

Analytical method development

Determination of λ max

100mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 100 ml volumetric flask and made it up to 100ml with the media (Secondary stock solution–100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of calibration curve

100mg of pure drug was dissolved in 10ml methanol (Primary stock solution - 1000 µg/ml). From this primary stock solution 10 ml was pipette out into 100 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Indian Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Formulation development of Tablets

All the formulations were compress by direct compression. The compositions of different formulations are given in Table 7.4.The tablets were prepared as per the procedure given below and aim is to prolong the release of Flurbiprofen. Total weight of the tablet was considered as 300mg.

Procedure

1) Flurbiprofen and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 3: Ingredients and Uses

Ingredients	Uses
Flurbiprofen	API
Tragacanth	Binding Agent
Acacia gum	Binding Agent
Xanthan gum	Binding Agent
PVP-K 30	Binding Agent
Aerosil	Anticaking agent
Magnesium Stearate	Lubricant
Lactose	Diluent

Table 4: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flurbiprofen	100	100	100	100	100	100	100	100	100
Tragacanth	50	100	150	-	-	-	-	-	-
Acacia gum	-	-	-	50	100	150	-	-	-
Xanthan gum	-	-	-	-	-	-	50	100	150
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	131	81	31	131	81	31	131	81	31
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the

following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

***In vitro* drug release studies**

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl, p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,9,10,11,12
Temperature	--	37°C $\pm$ 0.5°C

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus–II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer at 246nm.

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$\mathbf{F = K_o\, t}$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\mathbf{Log\ (100\text{-}F) = kt}$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$\mathbf{F = k\ t1/2}$$

Where, 'k' is the Higuchi constant.
In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$\mathbf{M_t/\ M_\infty = K\ t^n}$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION

The present study was aimed to developing sustained release tablets of Flurbiprofen using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release study.

Analytical method

Graphs of Flurbiprofen were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 246nm and 268nm respectively.

Table 5: Observations for graph of Flurbiprofen in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.165
10	0.312
15	0.449
20	0.586
25	0.698

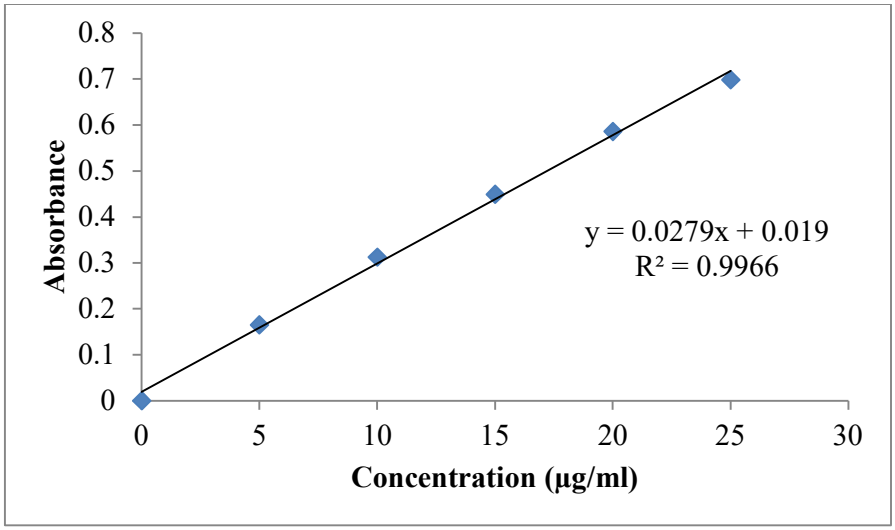

Fig 2: Standard curve of Flurbiprofen

Table 6: Standard graph values of Flurbiprofen at 268 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.173
10	0.324
15	0.468
20	0.598
25	0.751

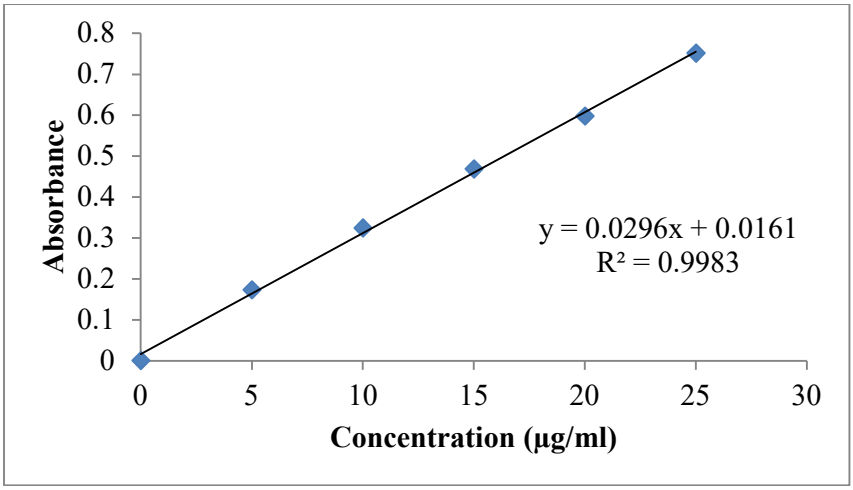

Fig 3: Standard curve of Flurbiprofen

Preformulation parameters of powder blend

Table 7: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.76±0.3	0.53±0.01	0.61±0.01	10.91±0.8	1.17±0.02
F2	24.87±0.3	0.55±0.01	0.65±0.03	10.63±0.5	1.15±0.03
F3	25.56±0.2	0.57±0.06	0.69±0.03	10.34±1.0	1.13±0.06
F4	23.20±0.1	0.54±0.21	0.67±0.12	10.83±0.5	1.11±0.06
F5	22.46±0.1	0.61±0.02	0.55±0.02	11.53±0.8	1.15±0.05
F6	23.19±0.2	0.58±0.04	0.63±0.04	11.24±0.6	1.19±0.03
F7	26.94±0.1	0.59±0.04	0.64±0.05	10.72±0.7	1.14±0.09
F8	23.67±0.3	0.56±0.12	0.58±0.04	10.43±1.0	1.18±0.07
F9	24.34±0.4	0.52±0.02	0.56±0.01	10.13±0.8	1.16±0.02

All the values represent n=3

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties.

Evaluation of tablets

Physical evaluation of Piracetam immediate release tablets

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 10.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 4.1- 5.6 kg/cm^2 and the friability values were < than 0.68 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.11- 3.87 mm. All the formulations satisfied the content of the drug as they contained 97.24-99.21 % of Piracetam and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 8: Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	300.02	5.3	0.51	3.11	98.32
F2	299.87	5.5	0.45	3.49	99.57
F3	296.50	5.7	0.39	3.77	100.00
F4	299.75	6.8	0.38	3.82	95.94
F5	299.85	5.9	0.26	3.58	96.57
F6	300.05	6.4	0.22	3.25	99.61
F7	297.61	5.6	0.44	3.28	97.44
F8	298.47	5.1	0.57	3.91	98.12
F9	299.83	5.8	0.43	3.32	95.80

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 296.50 to 300.05 mg, so the permissible limit is ±7.5% (>300 mg). The results of the test showed that, the tablet weights were within the limit.

Hardness test

Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 5.1 to 6.8 kg/cm^2, which was within IP limits.

Thickness

Thickness of five tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 3.11 to 3.91 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table-8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.80 – 100.00 %.

***In vitro* drug release studies**

Table 9: Dissolution data of Flurbiprofen tablets F1-F9

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	34.81	36.14	25.38	20.65	17.31	17.38	15.38	20.21	15.31
2	41.20	39.63	32.79	22.16	20.23	25.43	24.45	21.07	23.03
3	48.39	41.82	46.88	33.98	25.96	36.86	28.59	24.17	25.12
4	55.85	54.40	49.54	46.29	38.35	37.75	36.83	33.56	30.13
5	62.34	57.09	53.17	59.73	43.02	44.46	49.26	46.58	37.09
6	69.13	68.46	66.62	68.22	56.75	55.13	53.15	54.27	45.17
7	76.91	75.02	75.93	71.73	59.13	68.16	66.29	59.68	59.24
8	83.28	79.59	78.87	75.40	64.84	69.77	67.76	66.37	63.36
9	91.96	82.36	81.26	87.01	72.22	72.85	70.27	72.77	64.81
10	95.21	85.11	84.15	89.58	80.09	84.49	74.19	75.42	73.63
11	98.56	96.78	89.02	91.96	83.56	88.88	80.64	84.12	79.43
12		95.19	90.14	92.63	94.75	93.16	90.49	89.28	85.19

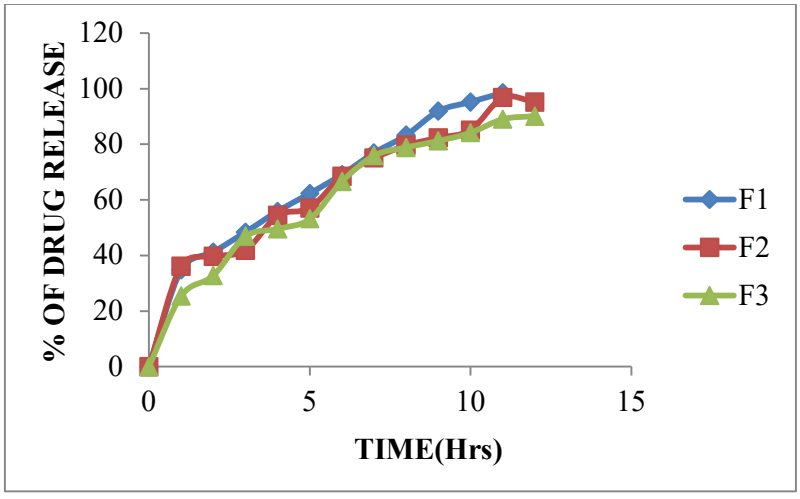

Fig 4: Dissolution profile of Flurbiprofen (F1, F2 and F3 formulations)

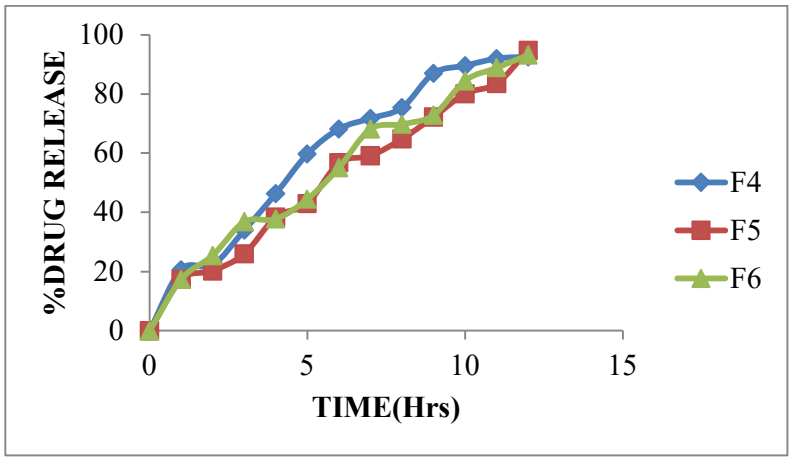

Fig 5: Dissolution profile of Flurbiprofen (F4, F5 and F6 formulations)

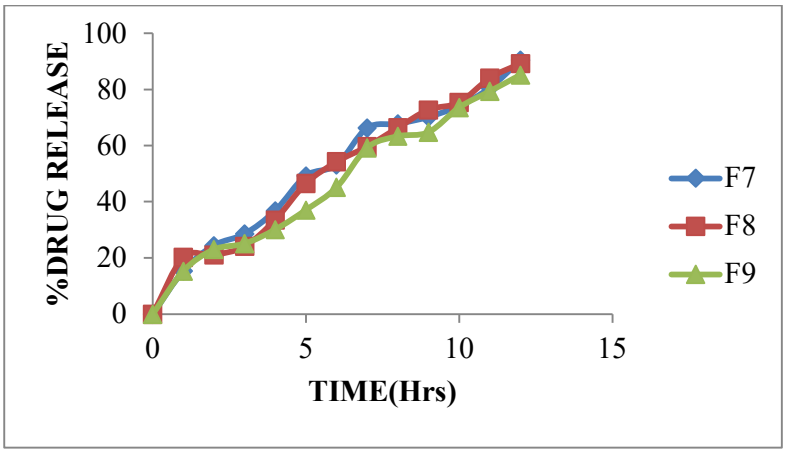

Fig 6: Dissolution profile of Flurbiprofen (F7, F8 and F9 formulations)

Different formulations (F1-F9) were prepared using different polymers like Tragacanth, Acacia gum and Xanthan gum alone at different ratios. Formulations F1-I3 were prepared using Tragacanth at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 98.56 % at 11h, 95.19% at 12h and 90.14 at 12h %.

Drug – Excipient compatibility studies

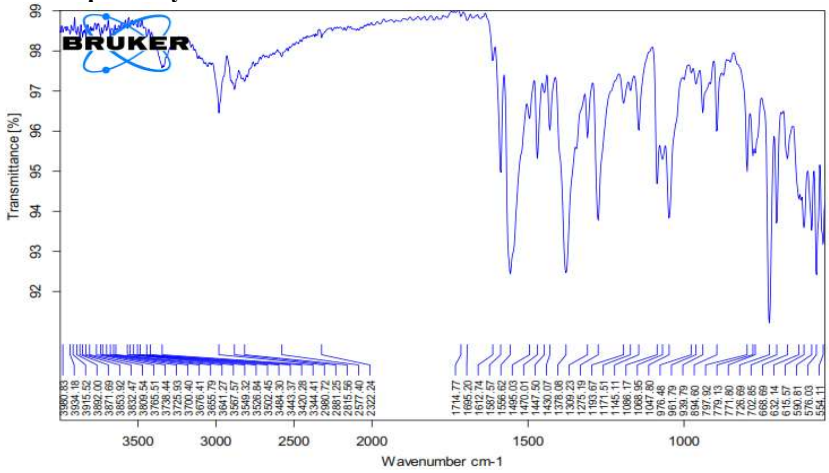

Fig 7: FT-TR Spectrum of Flurbiprofen pure drug

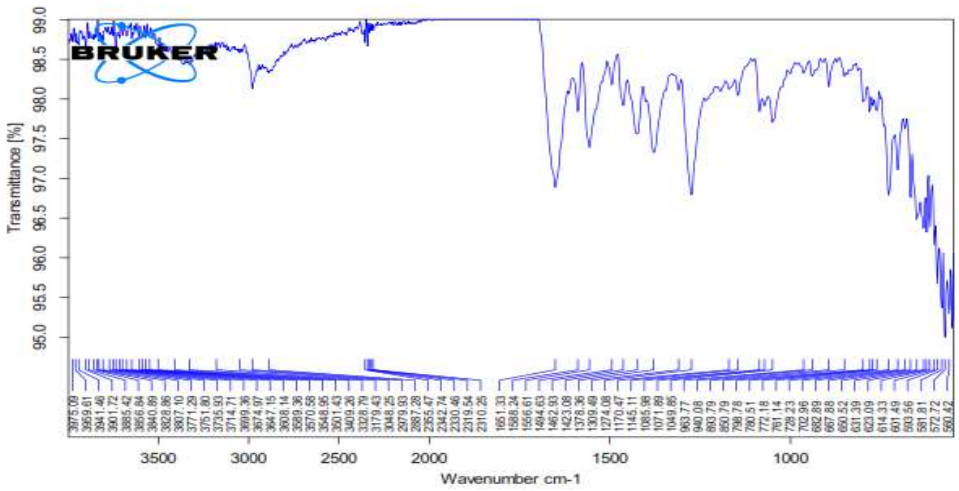

Fig 8: FT-IR Spectrum of Optimized Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Flurbiprofen and excipients used in the preparation of different Flurbiprofen Sustained release formulations. Therefore the drug and excipients are compatible to form stable.

CONCLUSION

The present study was carried out to evaluate the natural polymers for its matrix forming ability due to formation of thick gel structure, so we concluded that Tragacanth, Acacia gum and Xanthan gum formulated tablets were found to be effective in sustaining the drug release up to 12 hrs. During this study, it was also found that polymer concentration influences the drug release behaviour. Drug Excipient Compatibility studies revealed that there was no considerable change. FT-IR studies resulted that all peaks corresponding to different functional groups of pure drug were presents in the drug-excipient mixture no interaction between the drug and excipients. It can be concluded that stable formulation could be developed by incorporating Tragacanth polymer in a definite proportion, so that the sustained released profile is maintained for a sustained release. Release model of sample was found to follow Higuchi release kinetics mechanism with high linearity.

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