Section A-Research paper
ISSN 2063-5346

FORMULATION AND OPTIMIZATION OF NOVEL FAST DISSOLVING TABLET USING HIBISCUS ROSA-SINENSIS AS A SUPERDISINTEGRANT

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ABSTRACT
Natural polymers remain attractive primarily because they are natural products of plants, readily available, inexpensive and capable of multitude of chemical modification. Leaves of Hibiscus rosa-sinensis Linn (family: Malvaceae) contains high proportion of mucilage which can be used as additives in pharmaceutical formulations. The present work is to formulate and to optimize novel fast dissolving tablet containing Ketorolac Tromethamine using natural disintegrants isolated from Hibiscus rosa- sinensis leaves and its efficiency was compared with synthetic superdisintegrants like crosspovidone. Hibiscus rosa-sinensis mucilage was isolated and characterised for its identification by chemical test and micrometric properties. Fast dissolving tablets of ketorolac Tromethamine is going to be formulated by direct compression method using Hibiscus rosa-sinensis as super disintegrating, mouth freshener and compressibility and aspartame as sweetener. The tablets which are going to formulate were evaluated for their pre and post compression parameters like tablet hardness, thickness, % friability, wetting time they should be permissible limits.

Keywords: Novel Formulation Natural Disintegrants mild and Moderate Pain

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetics) and sudden episodes of coughing during the common cold, allergic condition and bronchitis [1].

For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate

instantaneously releasing the drug which dissolve or disperses in the saliva [2]. The faster the drug into solution, quicker the absorption and onset of clinical effect some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics [3].

Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of Superdisintegrants like cross linked Carboxymethyl cellulose, Sodium starch glycolate, Polyvinylpyrrolidone etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet moulding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

Concept of fast dissolving drug delivery system:-

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional means of taking their medication. Because of physiological changes associated with, especially, elderly and paediatrics are quite unable to swallow (Dysphasia); rather, this is a common problem of all age groups patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the paediatric and geriatric population, as well as other patients who prefer the convenience of easily swallow able dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva [4].

Recently, pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such patients. A tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet) is an attractive dosage form and a patient-oriented pharmaceutical preparation [5].

The mouth-dissolving tablets have attracted the interest of many researchers. Many elderly patients have difficulty swallowing tablets, capsules, or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The

disintegrated mass can slide down smoothly along the oesophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease .

There are two different types of dispersible tablets which have to be distinguished. One dosage form disintegrates instantaneously in the mouth to be swallowed without the need for drinking water while the other tablet formulation can readily be dispersed in water to form dispersion, easy to ingest by the patient [6]

Criteria for Fast dissolving Drug Delivery System:-

The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds. Be compatible with taste masking. Be portable without fragility concern. Have a pleasant mouth feel. Leave minimum or no residue in the mouth after oral administration. Exhibit low sensitive to environmental condition as temperature and humidity Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost [7].

Advantages of Fast Dissolving Tablet [8]

- Fast dissolving tablets (FDTs) are solid unit dosage form, so they provide precise dosing, and high drug loading is sanctioned in it, and it is an ideal dosage in case of geriatric and pediatric patients, and additionally it is an ideal alternative of conventional tablet.
- It has fast action, as it is taken by the patient, it commences melting when it comes in contact with saliva, it rapidly absorbed in the oral cavity, and it rapidly melts and produces fast action.
- Due to pregastric absorption, the bioavailability of the drugs is amended, and fewer doses are required, which amends the patient compliance, clinical reports are also amended.
- Fast dissolving tablets do not require water to swallow, and also they can be taken anywhere at any time, and they are a convenient option for travelling patients and diligent peoples who do not have immediate access of water; hence, patient compliance is amended.
- They are very facile and convenient to administer as they are a solid unit dosage form, and they are mainly convenient for geriatric, pediatric, uncooperative patients and dysphasic patients.
- Fast dissolving tablets are very safe and facile to swallow because there is no peril of suffocation in the airways due to physical obstruction during swallowing.

Materials and Methods

The drug is purchased from Rajshi Farma Private limited Delhi, the polymer Crospovidone is purchased from Kayel Medichem Pvt Ltd Delhi, Mannitol Aspartame, Talc and Magnesium Stearate is buy from Sigma Aldrich

Isolation and characterization of Hibiscus Rosa-Sinensis

Isolation and Characterization of Mucilage form Hibiscus rosa-sinensis the leaves of hibiscus Rosa-Sinensis linn were collected, from local market Meerut. The fresh hibiscus rosa-sinensis linn leaves were collected and washed with water to remove dirts and debries. Leaves were powdered and soaked in water for 5-6 hrs, boiled for 30 minutes and left stand for 1hours to allow complete release of mucilage into water. The mucilage was extracted using multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at.[9].

Preformulation Studies:-

Standardization of Drug:-

UV Spectrophotometric method for Ketorolac:-

Standard Calibration Curve of Ketorolac at 310 nm in pH 7.4 phosphate buffer by using UV Spectroscopy Method.

Physical drug Excipients Compatibility Studies:-

Fourier transforms infrared spectroscopy:-

FTIR study was performed to verify pure drug and polymer interaction. The study of pure drug and hibiscus rosa-sinensis, Crospovidone, Fenugreek Gum, The pure drug powder within potassium bromide and pellet was prepared by high pressure to 100kg/cm for 2min. The obtained tablet was investigate in FTIR 8400S, Shimadzu. KBr was investigated of samples. The process was repeated for determine of drug and Polymers.

DSC Studies:

The DSC thermo gram of physical mixture of Ketorolac and the polymers showed no characteristic peaks of polymers and Ketorolac peaks were still present but slightly shifted from their original positions

Melting Point Determination:-

Melting point determination was done by using capillary tube.

Solubility:

In water soluble (0.3551 mg/L at 25 °C) but display special solubility in 0.1M HCl.

Micrometry study of Powder:

Bulk density and tapped density:

Bulk density is calculated by adding know mass powder to a cylinder. The density is calculated as mass. Tapped density in this method firstly we have to weigh the known powder and then known powder transfer in a 10ml mechanically tapping cylinder. The tapping is started until the little further volume change is observed.

$$\text{LBD} = \text{Wt powder}/\text{Vol powder} \quad \ldots\ldots. \quad (1)$$

$$\text{TBD} = \text{Powder wt}/\text{Tapped vol powder} \quad \ldots\ldots.. \quad (2)$$

Carr's index:

The fast dissolving of powder can be determined by differentiate LBD & TBD of powder & value at which crowded depressed [10].

Carr's index is deliberate by formula:-

$$\% \text{ Carr's index} = \frac{\text{TBD}-\text{LBD}}{\text{TBD}} \times 100 \quad \ldots\ldots. \quad (3)$$

2.2.5.3 Hausner's ratio:

The Hausner's proportion of compose fast dissolving tablets dried power merge were resolve following equation [11].

$$\text{Hausner's ratio} = \frac{\text{TBD}}{\text{LBD}} \quad \ldots\ldots. \quad (4)$$

2.2.5.4 Angle of repose:

Angle of repose was investigated by using funnel method of following formula [11].

$$\text{Tan}\theta = \frac{\text{H}}{\text{R}} \quad \ldots\ldots. \quad (5)$$

Where,

θ = angle of repose

H = height of the pile

R= radius of the pile base

Preparation of Fast Dissolving Tablets of Ketorolac:

Fast Dissolving tablet containing Ketorolac were prepared by direct compression method by Containing 10 mg Ketorolac and polymers like (Hibiscus rosa-sinensis, Crospovidone, and Fenugreek Gum) were mixed completely using mortar & pestle. The Superdisintegrants were used in different proportions and in different combinations. All the ingredients were weighed accordingly specified in the formulation and mixed well except magnesium Stearate. Then the blend was passed through sieve no 60 which was used for the evaluation of flow properties. To the mixed blend of powder and excipients finally add magnesium stearate and then mixed for 5 min. The mixed blend was compressed with eight station tablet punching machine using 9.5 mm flat punches with break line. Four punches in the 9.5 mm station compressor are fixed with die cavity and remaining is fixed with dummy punches.

Evaluation Parameters of Compressed Tablet [12]

Tablet Hardness:

Tablet hardness is laboratory techniques in this technique we have check the hardness of tablets in case of storage and handling before usage. The hardness of the tablets we can perform by using the hardness tester like Monsanto hardness tester, 6 tablets each batch crushing with known weight was recorded in kg/cm2 and average weight was calculated**.**

Tablet Thickness [13]

Tablet thickness is done for equality of tablet size. Tablet thickness would be control within a 5 percent difference of standard value. 20 tablets taken from the batch and individual tablet thickness was measured with using digital vernier

2.4.3 Friability [14]

Friability is defined as it is capacity of a solid material break into smaller pieces in case of transportation. Friability follows the following procedure. Firstly 20 tablet taken and weight accurately and place in a plastic chamber and set the chamber at 25 rpm for 4 minutes, after the 4 min and 100 revolutions stop the Roche apparatus and reweight the 20 tablets and Calculate the loss in tablet weight by the following formula

F = Initial wt - Final wt/Initial wt × 100 ……. (6)

Weight variation:

This method is performed as weight variation of tablets. Twenty tablets were individually weighed in (gm) on electronic balance. After that calculated the average weight of tablet and checked for weight variation of tablets.

Calculation of percentage weight deviation:-

% Variation = Individual wt - Average wt/Average wt × 100 ……. (7)

Wetting Time

A piece of tissue paper folded twice was placed in a small Petridis of 6.5cm in diameter containing 6ml of water. A pre weighed tablet was placed on the surface of tissue paper and allowed to completely wet. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. The wetted tablet was then weighed. Water absorption ratio (R) was determined using the following equation [15, 16].

$$R = Wa\text{-}Wa/\ Wb\ X\ 100 \quad \ldots\ldots. \quad (8)$$

Where,

Wb - Weight of tablet before wetting.

Wa - Weight of tablet after wetting.

Dispersion Time:

Tablet was placed in 10 ml phosphate buffer pH 6.8 solution. Time required for complete dispersion of tablet was measured.

In-vitro dissolution studies:

In-vitro dissolution study was performed by using dissolution test apparatus (Veego) at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which time interval (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (Lab India UV 3000) by measuring the absorbance of the sample at ketorolac at 310 nm in pH 7.4 phosphate buffer by using UV Spectroscopy Method and Cumulative percentage drug releases are determined. Maintained at 37±0.50C Aliquot of dissolution medium (5 ml) was withdrawn at specific. The following procedure was employed throughout the study to determine the in vitro dissolution rate for all the formulations.

Dissolution parameters:-

Apparatus used - Veego

Temperature - 37± 0.50C

RPM - 50 rpm

Volume withdrawn - 5 ml for 5 minutes
λ max - 310nm

Stability studies:

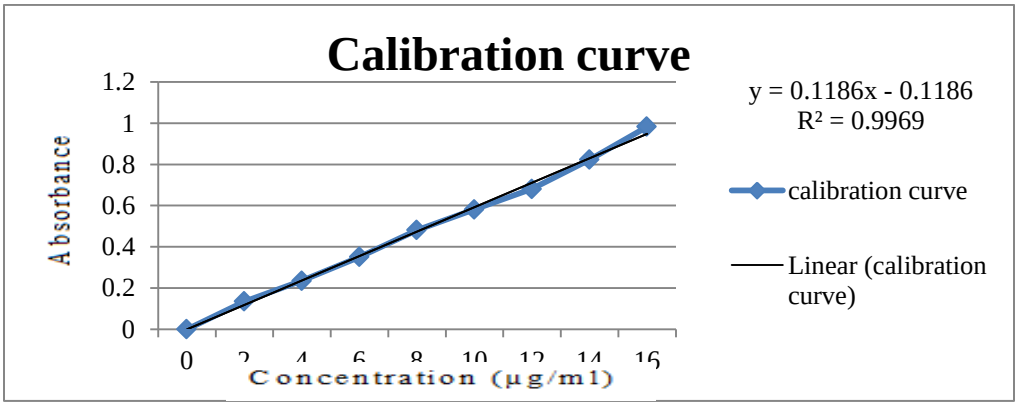
The stability studies of optimised formulation were carried out according to ICH guideline. The correct formulation was subjected to stability at 40±2°C/75±5% RH for 90 days. After then duration the product was evaluated for Colour, Hardness, Disintegration time & In-vitro release [17].

RESULT AND DISCUSSION

Preformulation Study-

UV Spectroscopy-

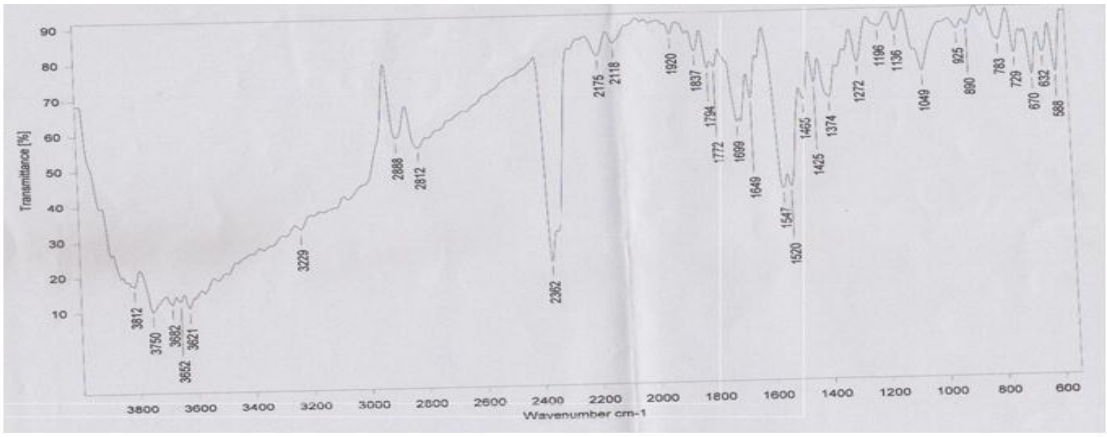
After scanning of the sample drug, the wave length was obtained about 310 nm in pH 7.4 phosphate buffers by using UV Spectroscopy Method Figure 3.1.



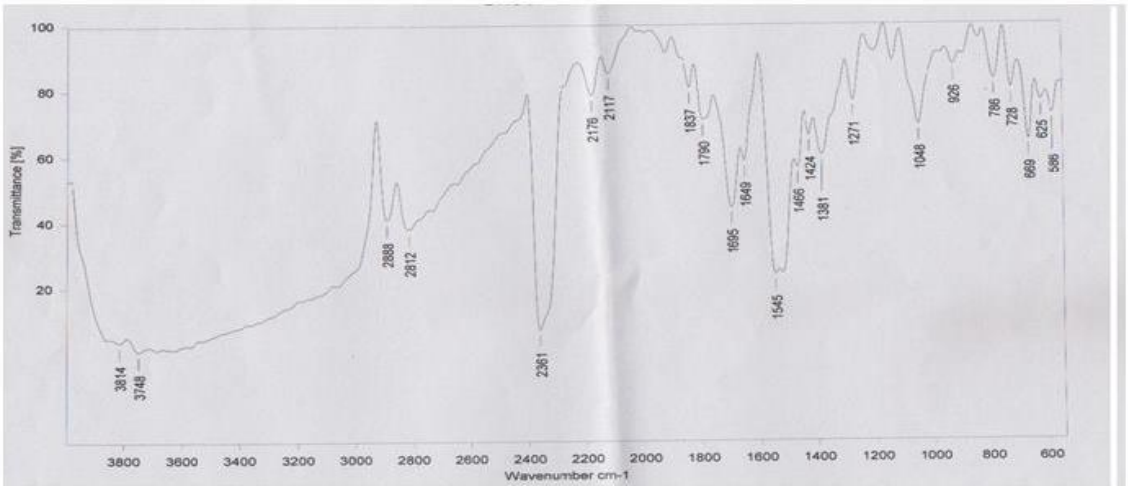
Graph 1 Standard Calibration Curve of Ketorolac Tromethamine

Physical drug Excipients Compatibility Studies:-

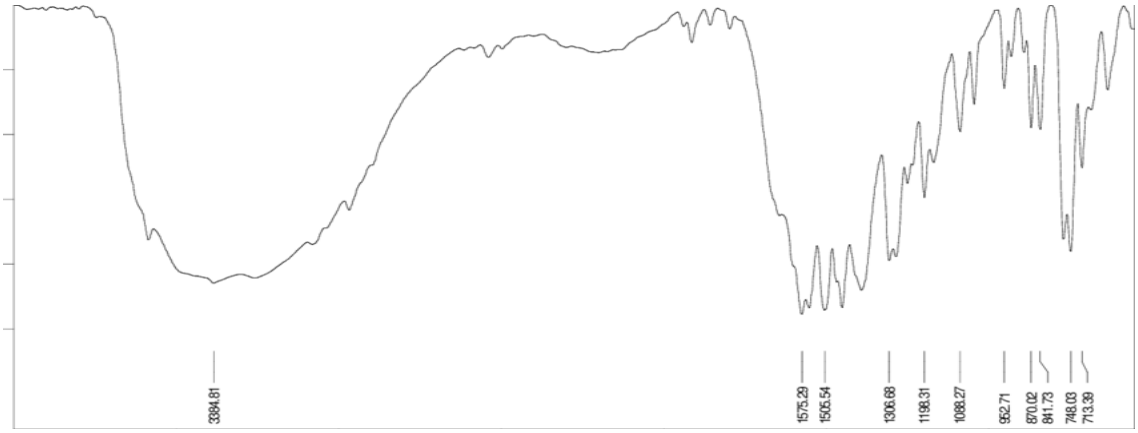
FTIR:-



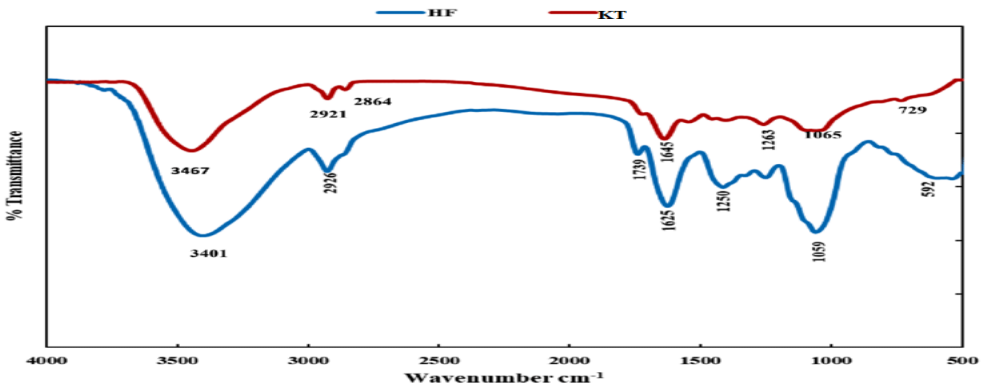
Graph 2 FTIR spectrum of Ketorolac Tromethamine



Graph 3 FTIR spectrum of Ketorolac Tromethamine with Fenugreek Gum



Graph 4 FTIR spectrum of Ketorolac Tromethamine with Crospovidone



Graph 5 FTIR spectrum of Ketorolac Tromethamine with Hibiscus Rosa

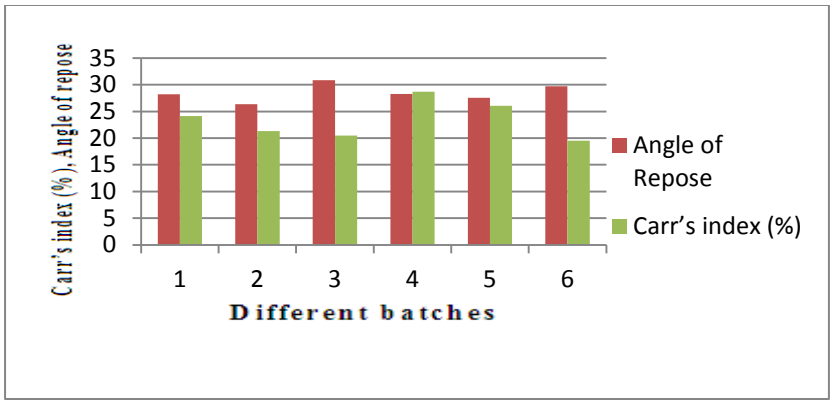
Discussion FTIR Spectroscopy:-

Table 2 FT-IR Spectral Data of Pure Ketorolac Tromethamine with Excipients

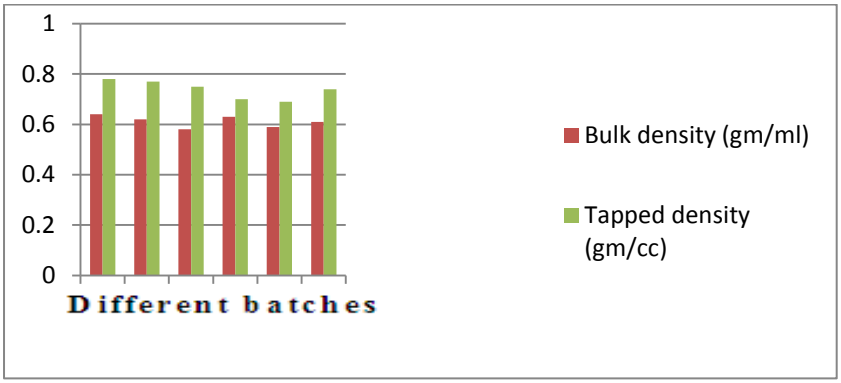
S.No.	Wave Number (cm^1)	Functional Group
A	**Ketorolac Tromethamine**	
1	3406	Broad band of bonded OH
2	1637	C=O of aryl acids stretching
3	1459	C=N stretching
4	1419	Aromatic C=C stretching
5	1081	C-N stretching
6	755	CH_3 angular
B	**Ketorolac Tromethamine with fenugreek Gum**	
1	3422	Broad band of bonded OH
2	2132	C-H Stretching for methyl
3	1640	C-N vibration
	1532	C=C stretching
4	1279	C=N stretching
5	510	Aromatic
C	**Ketorolac Tromethamine with Crospovidone**	
1	3484	OH Stretching
2	3409	Aliphatic C-H
3	2942	C=O Stretching
4	2708	C-N Stretching
5	751	C-H Methane
6	440	CH2 Group

Evaluation of Powders for Fast Dissolving Tablet

The physical mixtures for fast dissolving tablet were evaluated with respect to Angle of repose was found between 26.36±1.06 to 30.86±0.48and Carr's index values were found 24.15±1.9 to 19.50±0.8% the powder of all batches excellent to poor flow ability and compressibility. Hausner ratio was found to be 1.26±0.14to 1.31±0.12. Bulk density ratio 0.58±0.44 to 0.64±0.68 and tapped density ratio 0.64±0.68to 0.61±0.54 for all the batches indicating that possible and poor flow properties.



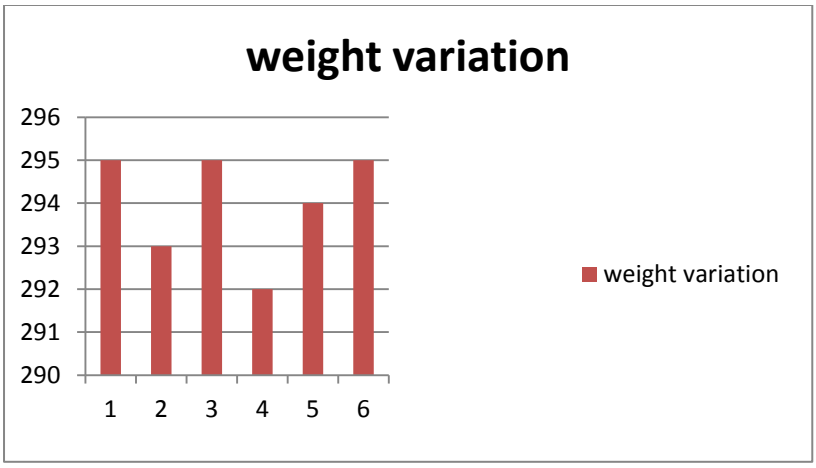
Graph 5Graphical representation of Carr's index and Angle of repose found in different batches of formulation



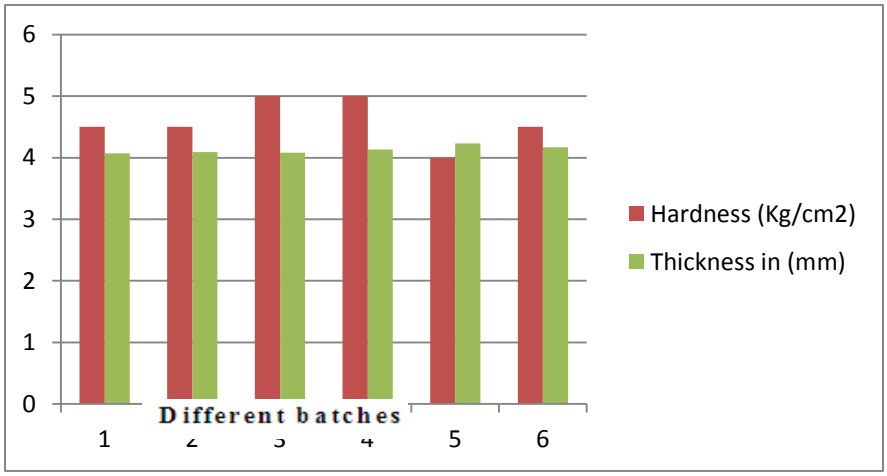
Graph 6 Graphical representations of Bulk density and Tapped density found in different batches of formulation

Evaluation Parameters of Compressed Tablet:

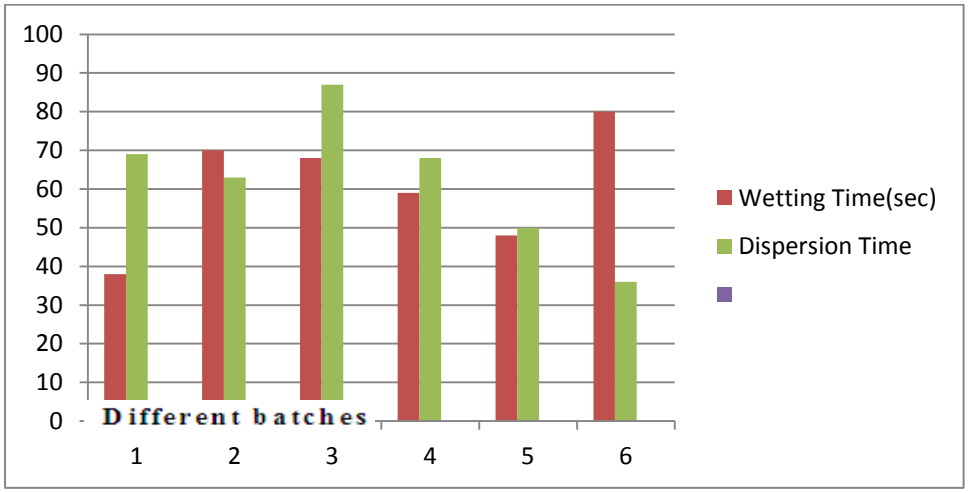
The physical parameters Hardness of tablets were found to 3.78 to 5.5 kg/cm2. The friability of all prepared tablets was found to 0.32% to 0.48 %. The Thickness was found range 4.01±0.4 to 4.12±0.4 mm. The weight variations of all tablets were established to be 195 to 195 to 197 mg. The Wetting time 23±1 to 62±1, disintegration 31±1 to 31±1, and Dispersion Time found to be about 23±1 to 62±1.



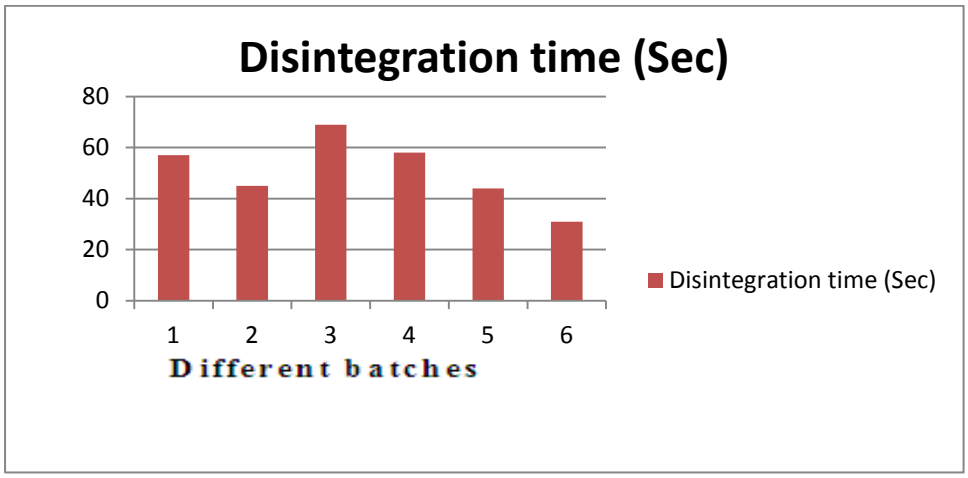
Graph 7 Graphical representation of Weight variation found in different batches of formulation



Graph 8 Graphical representations of Hardness and Thickness found in different batches of formulation



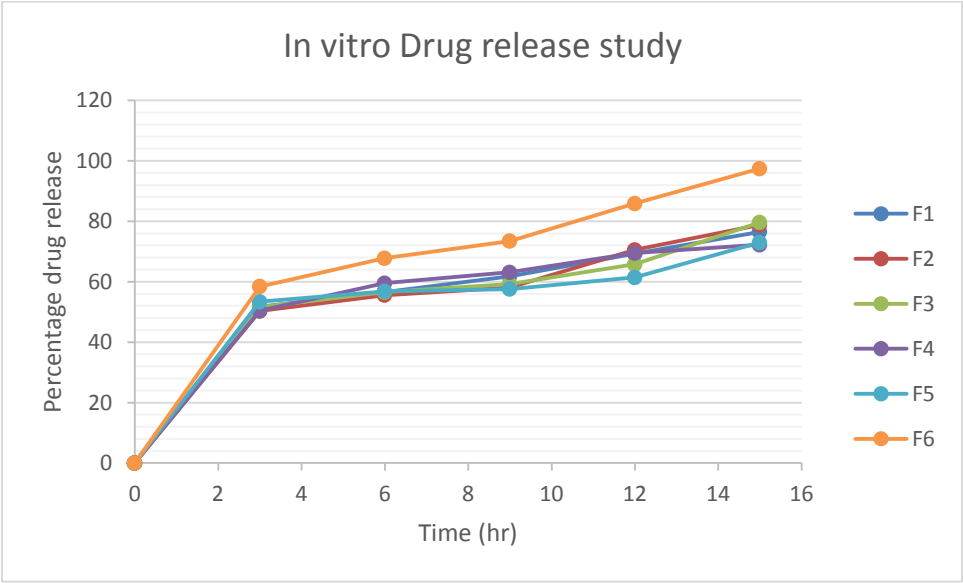
Graph 9 Graphical representation of wetting time and Water absorptions found in different batches of formulation



Graph 10 Graphical representation of Disintegration time found in different batches of formulation

In-Vitro Drug Release Studies:

The percentage of drug released from the formulation F1, F2 and F3 was found to be 51.65±2.2 to 75.59±0.5% and 49.3±0.27% to 77.68±1.24and 49.04±0. 71.98±0.9 The % of drug Released from the formulations F4, 5 and 6 was found to be 50.25±0.21to 78.8±0.91%, 51.4±0.62 to 73.97±1.30% and F6, 59.41±1.30to 97.12±0.94% for respectively. It was observed that The formulation F6 containing best concentration of Superdisintegrants than the other formulations so it is give the batter release within 15min than the other formulations.



Graph 11 Cumulative Percentage drug release of Ketorolac Tromethamine

Stability Studies:

Table 3.7 Stability study for best formulation F6

S.No.	Parameters	Initial	1 Month	2 Month	3 Month
1	Colour	White	No Change	No Change	No Change
2	Hardness**(Kg/cm2)**	4.5	4.62	4.78	4.97
3	Disintegration time (sec)	31±1 (sec)	31±1 (sec)	31.6±1 (sec)	31.9±1 (sec)
4	In-Vitro Drug Release	97.12±0.94	97.02±0.96	96.87±0.071	96±1.04

Discussion:

The duration of stability studies of the Formulation 6, there is no change in colour, but found the minor variation in hardness, Disintegration time and In vitro drug release. All data evaluated according to ICH guidelines at 40±2°C/75±5% RH for 90 days.

Conclusion

The Fast disintegrating tablets of Ketorolac Tromethamine were prepared by dry granulation method using different Superdisintegrants such as Hibiscus Rosa-Sinensis, Fenugreek gum, and in different concentration, prepare Coground mixtures of Hibiscus Rosa-Sinensis, Crospovidone and Mannitol to improve the compatibility and stability of product. The FTIR, DSC analysis revealed that the Ketorolac Tromethamine and polymer used were compatible with Ketorolac Tromethamine. Disintegration time decrease with increase in the concentration of Superdisintegrants Among all formulation, Hibiscus Rosa-Sinensis (in concentration 15, 24 mg), as Superdisintegrants is fulfilling all the parameters satisfactorily. In vitro release studies that almost 97.45 % of drug was release from formulation F6 within 15 minutes in comparison to other formulation. Thus in this research, Hibiscus Rosa-Sinensis was found to play a most important role in fast release of drug, other disintegrants and Mannitol to improve the compatibility and stability of product. In present work fast dissolving tablets have been synthesized to overcome drawbacks associated with allergic.

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