DESIGN, OPTIMIZATION AND EVALUATION OF IBUPROFEN FAST DISSOLVING TABLETS EMPLOYING STARCH SUCCINATE BY WET GRANULATION METHOD

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Abstract: The main aim of the project is preparation, Optimization and Evaluation of Ibuprofen Fast Dissolving Tablets Employing Starch Succinate by Wet Granulation Method. Fast dissolving tablets containing 200mg of Ibuprofen could be prepared employing starch succinate and other known superdisintegrants, crospovidone and croscarmellose sodium by wet granulation technique. Hardness of the tablet was in the range of 3.6 - 4 kg/sq.cm. It indicates good strength with a capability to resist physical and prefunctionary stress conditions during handling. Weight loss on the friability test less than 0.15% in all cases. All the fast-dissolving tablets prepared contained ibuprofen within 100± 5% of the labelled claim. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. Starch succinate is an efficient superdisintegrant for fast dissolving tablets. The disintegration and dissolution efficiency of the fast-dissolving tablets of ibuprofen was good and depended on the concentration of superdisintegrants employed i.e., starch succinate, croscarmellose and crospovidone. The formulated fast dissolving tablets of ibuprofen exhibited good dissolution efficiency in 5min which can be used for the fast therapeutic action of ibuprofen.

Keywords: Design, Optimization, Evaluation, Ibuprofen, Fast Dissolving Tablets, Wet Granulation Method

Introduction:

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 pediatrics are quite unable to swallow (Dysphagia); 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 pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.[1]

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.[2] 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 esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease.[3] 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.[4]

Recently, the European Pharmacopoeia[5] adopted the term orodispersible tablet as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than 3 minutes. There was no specification concerning either the hardness or the friability of this kind of tablets. That is why we find certain Rapidly Disintegrating Tablets (RDT) in the market that disintegrate in less than 1 minute or maybe 30 seconds, but are brittle and require

specified peelable blister packaging and thus higher costs.[6]. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates quickly in the oral cavity upon the contact with saliva, resulting in solution or suspension of the administered medicine.[7] FDT dosage forms, also commonly known as fast melt, quick melt, orally disintegrating tablets, and orodispersible systems, have the unique property of disintegrating the tablet in the mouth in seconds.[8] Administration of bitter drugs orally with acceptable level of palatability is a key issue for healthcare providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals.[9] Taste masking of the drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer system or complexation.[10] Taste-masking technologies are increasingly focused on aggressively bitter-tasting drugs like the macrolide antibiotics, non-steroidal anti-inflammatory drugs, and penicillins. Taste masking of water-soluble bitter drugs, especially those with a high dose, is difficult to achieve by using sweeteners alone. As a consequence, more efficient techniques such as coating, microencapsulation, and granulation have been used in combination with the sweeteners.[11]

In 1953, Freudenberg et al.[12] got a patent for taste masking of bad taste of bromoisovaleryl urea by CD complexation. In that research, they described that only the dissolved substances elicit taste sensation and the substances which are completely insoluble in water are tasteless. In many cases, however, the drugs are so intensely bitter that they even at ppm levels are hardly tolerable.[13]

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.[14] The drugs belonging to Biopharmaceutical Classification System Class II, i.e., the drugs with poor solubility and high permeability are best suitable moieties for FDTs in a dose of 125 and 250 mg.[15,16] Tizanidine HCl,[1] Oxybutynin HCl,[2] Rofecoxib,[3] Ibuprofen,[4] Promethazine Theoclate,[17] prednisone,[18] Indomethacin,[19] Glyburide,[20] Fentanyl citrate,[21] Griseofulvin,[22] Hydrochlorothiazide,[23] Crystallized Paracetamol,[24] and Nimesulide[25] are few examples of drugs that has been formulated as fast-dissolving drug delivery system.

Ibuprofen is the most commonly used and most frequently prescribed NSAID. It is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). Although its anti inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclo-oxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever.
The main aim of the project is preparation, Optimization and Evaluation of Ibuprofen Fast Dissolving Tablets Employing Starch Succinate by Wet Granulation Method

Materials & Methods:

1. Ibuprofen (Yarrow Chemicals, Mumbai).
2. Starch succinate (Prepared in the Laboratory)
3. Crospovidone (Molychem, Mumbai).
4. Croscarmellose (Molychem, Mumbai).
5. Mannitol (Yarrow Chemicals, Mumbai).
6. Starch (Yarrow Chemicals, Mumbai).
7. Magnesium stearate (Molychem, Mumbai).
8. Talc (Molychem, Mumbai).

Preparation of Starch Succinate (A Novel Superdisintegrant)

Initially succinic acid was dissolved in distilled water and the pH is adjusted to 3.5 using 10M NaOH and finally made upto 50ml. To this potato starch was added and conditioned for 16 hrs, the product was kept in oven at 60ºC for 1hr. Then the product was washed with water to remove any unreacted succinic acid if present. After washing, the resultant starch succinate was kept in oven for 60ºC until it gets dried. The product obtained was ground and dried.

The starch succinate prepared was found to be fine, free flowing crystalline powder. It was insoluble in aqueous solvents and insoluble in organic solvents tested (methanol, petroleum ether, dichloromethane and chloroform) the pH of 0.1% aqueous dispersion was 3.98.

Starch succinate exhibited good swelling in water. The swelling index was 62.4% all micromeritic properties indicated good flow and compressibility needed for solid dosage from manufacturing. The density of starch succinate was found to be 0.481g/cc. The presence of peaks of absorption at 1204.42cm^{-1} characteristic peak of esters. So from FTIR studies it was concluded that starch succinate (ester) was formed when starch was allowed to react with succinic acid. The X-ray diffraction pattern of starch succinate showed characteristic peaks, which indicates that the structure is completely crystalline. The disappearance of pink color in the ester confirmed the presence of ester, i.e., starch succinate.

As the starch succinate was crystalline powder and it had got all the characteristics of super disintegrants it was concluded that starch succinate can be used as novel super disintegrant in the formulation of fast dissolving tablets.

Table: 1. Physical and Micromeritic Properties of the Starch Succinate Prepared

Parameters	**Observation**
Solubility	Freely soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and carbonates.
pH (1% w/v aqueous dispersion)	3.98
Melting point	Charred at 80ºC
Viscosity(1%w/v aqueous dispersion)	1.60 cps
Swelling index	62.4%
Gelling property	No gelling and the swollen particles of starch succinate separated from water. Where as in the case of starch, it was gelatinized and formed gel.
Moisture absorption	4.1%
Particle size	250 µm (80/120mesh)
Density	0.481 g/cc
Bulk density	0.495 g/cc
Angle of repose	25.2º
Compressibility index	9.17%

Preparation of Ibuprofen Fast Dissolving Tablets:

The tablets were prepared by direct compression method. For uniformity in particle size each ingredient was passed through # 100 mesh sized screen before mixing. Starch succinate, crospovidone, croscarmellose sodium, starch was accurately weighed and mixing using mortar and pestle, and then added to Ibuprofen. Finally, talc and magnesium stearate were added to the powder. Finally mixed blend was compressed by using eight station rotator press (Shakthi Machineries Pvt, Ltd, Ahmedabad, India).

Table: 2. Formulation of Ibuprofen Fast Dissolving Tablets Employing Starch Succinate Prepared by Wet Granulation Method.

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Ibuprofen	200	200	200	200	200	200	200	200
Starch succinate	---	50	---	50	---	50	---	50
Croscarmellose sodium	---	---	50	50	---	---	50	50
Crospovidone	---	---	---	---	50	50	50	50
Mannitol	270	220	220	170	220	170	170	220
Potato starch	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10
Total weight(mg)	500	500	500	500	500	500	500	500

Results:

Preparation of Standard Solution:

Ibuprofen (10mg) was dissolved in methanol in a 10ml of volumetric flask and diluted quantitatively with methanol to obtain a solution having a known concentration of 500µg/ml.

Procedure:

The standard solution of ibuprofen was subsequently diluted with pH 7.2 phosphate buffer to obtain a series of dilution containing 2, 4, 6, 8 and 10µg of Ibuprofen per ml of solution. The absorbance of these solutions was measured in UV-visible spectrophotometer (analytical technology T360) at 221nm using pH7.2 phosphate buffer.

Table: 3. Calibration Curve for the Estimation of Ibuprofen by UV Spectrophotometric Method.

Concentration(µg/ml)	Absorbance	RSD (%)
2	0.087	0.012
4	0.185	0.021
6	0.270	0.027
8	0.345	0.034
10	0.445	0.033

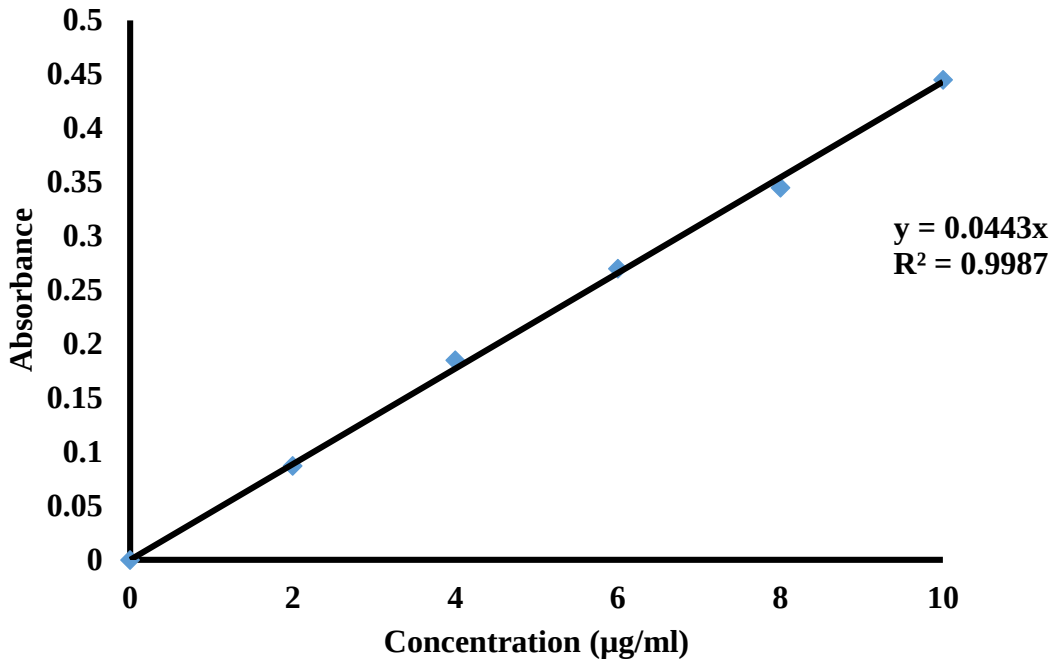

Fig.1. Calibration Curve of Ibuprofen by UV Spectrophotometric Method

Table: 4. Amounts of Ibuprofen Estimated in Interference Studies by UV Spectrophotometric Method

Excipient	Amount of Ibuprofen Added (mg)	Amount Estimated (mg)	Percent Estimated (Recovery)
Starch Succinate	200	199.85	99.25
Croscarmellose Sodium	200	199.98	99.99
Crospovidone	200	199.86	99.93
Mannitol	200	199.89	99.94
starch	200	199.78	99.89
Magnesium Stearate	200	199.95	99.97
Talc	200	199.91	99.95

The UV spectrophotometric method obeyed Beer's law in the concentration range of 2-10 µg/ml. Low RSD values ensured reproducibility of the method. The results given in Table: 5.2, indicated that the starch succinate and other excipients did not interfere in the method of estimation. Recovery of Ibuprofen from the physical mixture of drug and excipient was found to be 99.25 - 99.99 %. Thus the method was found to be suitable for the estimation of Ibuprofen content in various products and In-vitro dissolution studies in the present study.

Table: 5. Physical Properties: Hardness, Friability, Drug Content of Ibuprofen Fast Dissolving Tablets Prepared by Wet Granulation Method

Formulation	Hardness (Kg/Cm^2)n ± S.D	Friability (%) n ± S.D	Drug Content (Mg/Tab) n ± S.D	Disintegration Time (Sec) n ± S.D	Wetting Time (Sec) n ± S.D	Water Absorption Ratio (%) n ± S.D
F1	3.9± 0.01	0.12±0.013	198.89±0.71	132±03	100±0.51	42.9±0.52
F2	3.6± 0.03	0.13±0.015	199.10±0.79	32±02	20±0.12	50.0±0.55
F3	4.0± 0.01	0.14±0.012	198.82±0.63	50±02	42±0.23	68.0±0.04
F4	3.8± 0.04	0.12±0.014	199.56±0.55	42±03	31±0.19	51.5±0.21
F5	3.7± 0.03	0.14±0.014	199.13±0.56	45±04	29±0.16	52.9±0.52

F6	3.9± 0.01	0.15±0.012	199.21±0.21	30±02	21±0.14	58.0±0.02
F7	3.7± 0.02	0.14±0.014	198.02±0.57	32±03	19±0.16	31.4±0.01
F8	4.0± 0.04	0.12±0.013	199.32±0.11	15±02	15±0.11	48.9±0.01

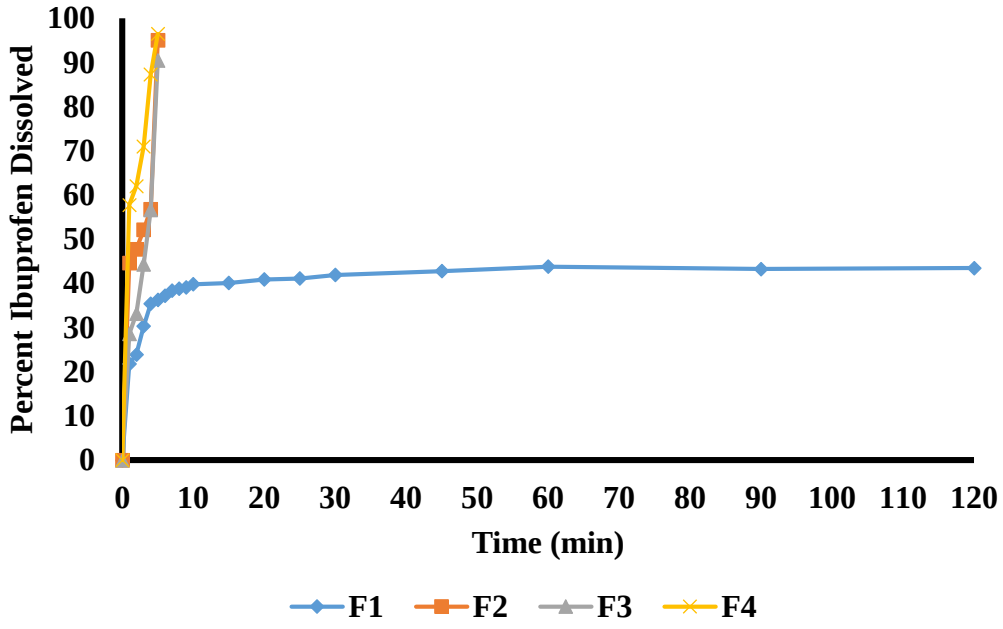

Fig 2: Dissolution Profiles of Ibuprofen Fast Dissolving Tablets Prepared Employing Starch Succinate (F1-F4)

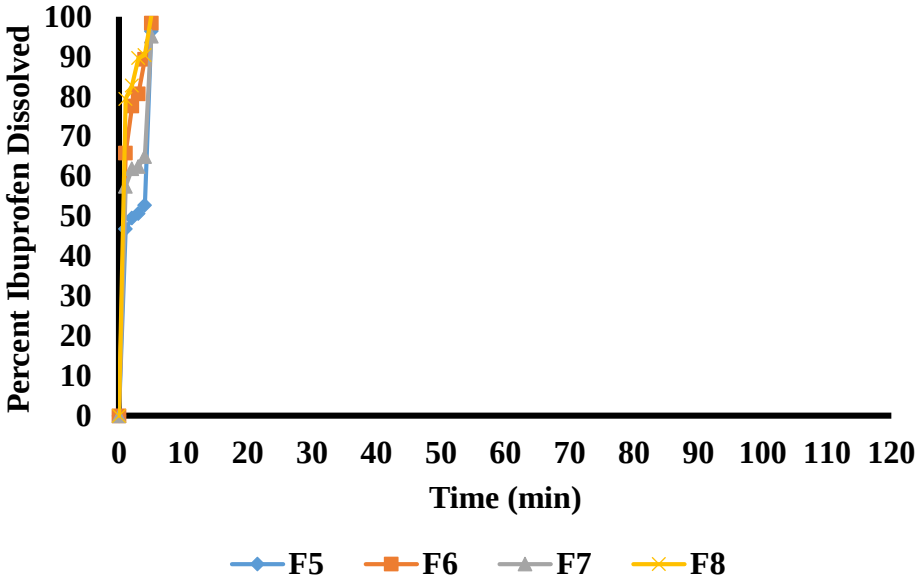

Fig3:Dissolution Profiles of Ibuprofen Fast Dissolving Tablets Prepared Employing Starch Succinate (F5-F8)

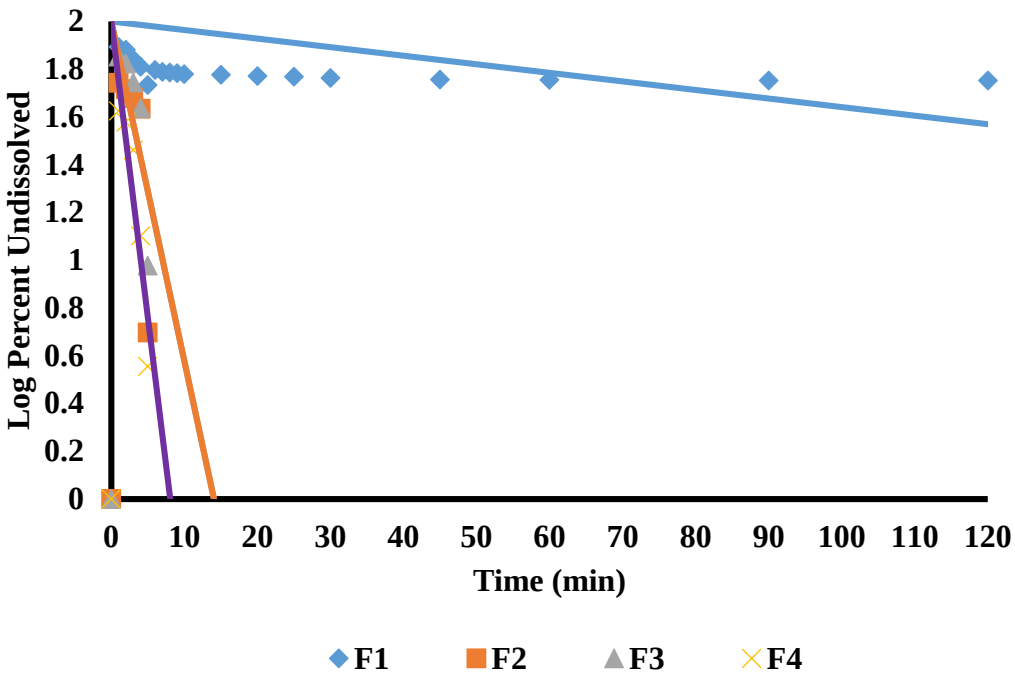

Fig 4: Time V_s Log Percent Undissolved Plots for Ibuprofen Dissolving Tablets Prepared Employing Starch Succinate (F1-F4)

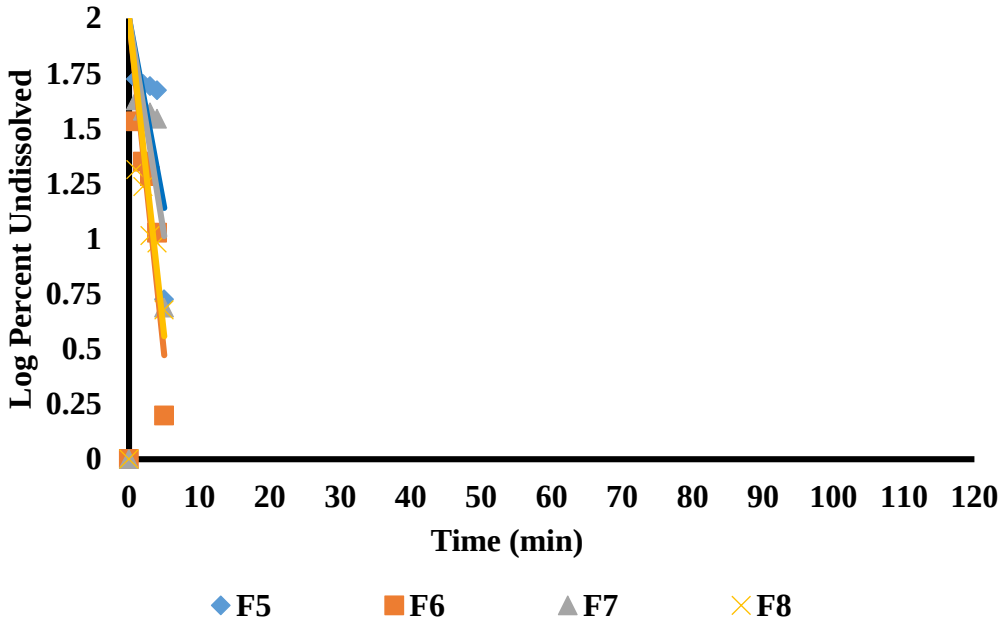

Fig 5: Time V_s Log Percent Undissolved Plots for Ibuprofen Fast Dissolving Tablets Prepared Employing Starch Succinate (F5- F8)

Fast dissolving tablets containing 200mg of Ibuprofen could be prepared employing starch succinate and other known superdisintegrants, crospovidone and croscarmellose sodium by wet granulation technique. Hardness of the tablet was in the range of 3.6 - 4 kg/sq.cm. It indicates good strength with a capability to resist physical and prefunctionary stress conditions during handling. Weight loss on the friability test less than 0.15% in all cases. All the fast dissolving tablets prepared contained ibuprofen with in 100± 5% of the labelled claim. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. The disintegration time of all the formulated to be in the range of 28 to 132 seconds as indicated in the Table.

To evaluate the individual and combined effects of the three factors involved, fast dissolving tablets were formulated employing selected combinations of the factors as per 2^3-factorial design. Fast dissolving tablets dissolution data analyzed as per ANOVA of 2^3-factorial design. ANOVA of fast disintegrating times indicated that the individual effects of starch succinate (A), croscarmellose sodium (B) and crospovidone (C) as well as the combined effects of AB, AC, BC and ABC factors on the disintegrating time of tablets were significant ($p<0.05$).

Table: 6. ANOVA of Disintegrating Times of Fast Dissolving Tablets Employing Starch Succinate

Source of Variation	D.F	S.S	M.S.S	Variance Ratio	Result
Replicates	2	19.09	9.545	11.51	P >0.05
Treatments	7	450.14	64.28	43.8	P <0.05
Starch succinate (A)	1	595.5	595.5	81.5	P <0.05
Croscarmellose (B)	1	992.66	992.66	97.4	P <0.05
Starch succinate x Croscarmellose (AB)	1	392.66	392.66	67.9	P <0.05
Crospovidone (C)	1	592.8	592.8	69.9	P <0.05
Starch succinate x Crospovidone (AC)	1	308.2	308.2	37.5	P <0.05
Croscarmellose x Crospovidone (BC)	1	126.1	126.1	21.71	P <0.05
Starch succinate x Croscarmellose x Crospovidone (ABC)	1	252.8	252.8	41.61	P <0.05
Error	14	11.61	0.829		
Total	23				

P <0.05 indicate significance; P >0.05 indicate non-significance

*D.F- Degrees of Freedom

*S.S- Sum of Squares

*M.S.S-Mean Sum of Squares

ANOVA of dissolution efficiency in 5min indicated that the individual effects as well as combined effects of the three factors (i.e., starch succinate, croscarmellose and crospovidone) were all significant ($p<0.05$). The ANOVA results, thus indicated that the three factors have significantly influence the disintegration time and dissolution efficiency in 5min.

Fast dissolving tablets formulated employing starch succinate (10%), croscarmellose (10%) and crospovidone (10%) as superdisintegrants exhibited fast disintegration and dissolution efficiency in 5min. Formulation 8 gave release of 100% in 5mins fulfilling the official specification, based on disintegration time and dissolution efficiency. Formulation 8 is considered as a good fast dissolving tablet formulation of ibuprofen.

Table: 7. ANOVA of Dissolution Efficiency in 5min of Fast Dissolving Tablets Formulated Employing Starch Succinate

Source of Variation	D.F	S.S	M.S.S	Variance Ratio	Result
Replicates	2	26.08	13.04	27.33	P >0.05
Treatments	7	855.2	79.54	53.0	P <0.05
Starch succinate(A)	1	413.3	413.3	67.4	P <0.05
Croscarmellose (B)	1	715.4	715.4	99.0	P <0.05
Starch succinate x Croscarmellose (AB)	1	478.8	478.8	38.5	P <0.05
Crospovidone (C)	1	820.4	820.4	15.55	P <0.05
Starch succinate x Crospovidone (AC)	1	150.4	150.4	31.53	P <0.05
Croscarmellose x Crospovidone (BC)	1	135.3	135.3	3.79	P <0.05
Starch succinate x Croscarmellose x Crospovidone (ABC)	1	478.8	478.8	38.46	P <0.05
Error	14	6.68			
Total	23				

P <0.05 indicate significance; P >0.05 indicate non-significance

*D.F- Degrees of Freedom.

*S.S- Sum of Squares.

*M.S.S- Mean Sum of Squares.

Stability Studies

Experimental The following formulation developed employing starch succinate by were subjected to stability testing:

Ibuprofen fast dissolving tablets, F_8 formulated employing starch succinate prepared by wet granulation method.

In the case the tablets were packed in screw capped HDPE bottles and were stored at 40ºC±2ºC and 75% RH for 6 months. After storage for 6 months, the products were tested for drug content and drug release rate as per methods described earlier.

Table: 8. Dissolution Profiles of Ibuprofen Fast Dissolving Tablets (F_8) Prepared by Wet Granulation, Before and After Storage for 6 months during the Stability Testing

Time (Min)	Percent Ibuprofen Dissolved (x ± s.d)	
	Before Storage	**After 6 Months**
1	79.42 ± 0. 11	78.98 ± 0. 13
2	82.78 ± 0. 23	82.11 ± 0. 27
3	89.65 ± 0. 25	88.99 ± 0. 25
4	90.41 ± 0. 33	90.11 ± 0. 33
5	99.81 ± 0. 22	99.12 ± 0. 22

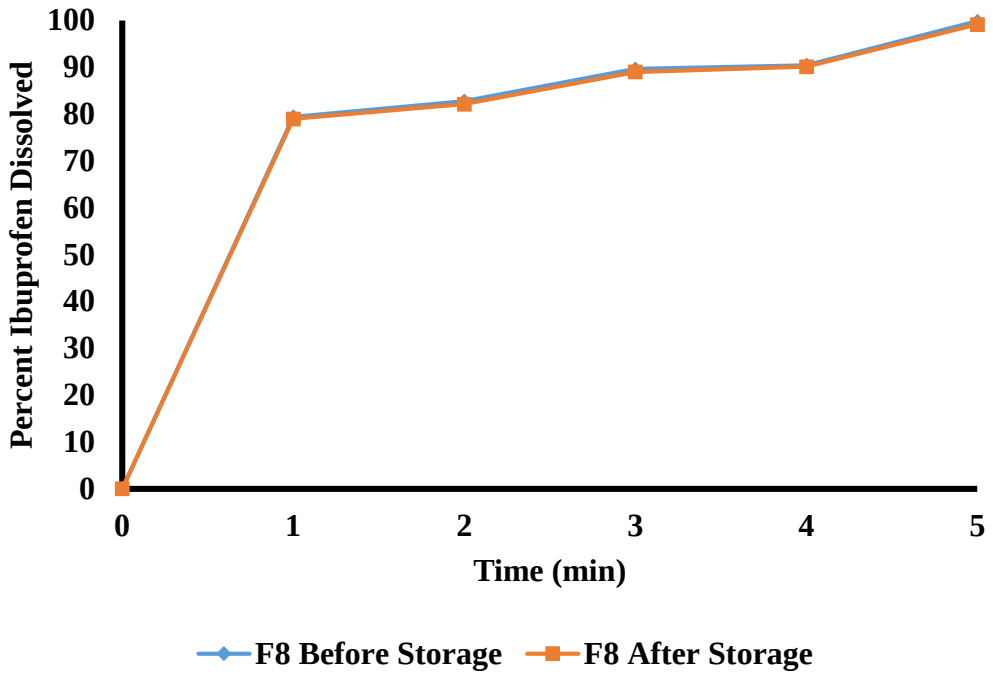

Fig 6: Dissolution Profiles of Ibuprofen Fast Dissolving Tablets (F_8) Prepared by Wet Granulation, Before and After Storage for 6 months During the Stability Testing

DISCUSSION

The compatibility of starch succinate with the selected drug (Ibuprofen) was evaluated by DSC, FTIR and TLC studies. The DSC thermograms of IB and IB-SS exhibited endothermic peaks at 79.77ºC and 79.02ºC respectively. These melting peaks of IB and IB-SS correspond to the melting point of ibuprofen (75°-78º C). The melting peaks observed in the DSC thermograms of ibuprofen and ibuprofen- SS mixtures correspond to the melting points of the respective drug indicating no interactions between the selected drug and starch succinate polymer. The DSC study thus indicated no interaction between starch succinate and selected drug.

The characteristic FTIR bands of ibuprofen at 2955.62 cm^{-1} (COOH), 1508.54 cm^{-1} (C=C), 1720.83 cm^{-1} (C=O) were all observed in the FTIR spectra of both IB and IB- SS. These FTIR spectral observations also indicated no interaction between starch succinate and the drug selected.

In the TLC study, single spots were observed in the case of pure drugs as well as their mixtures with starch succinate. The close agreement of the R_f values of the drugs and their mixtures with starch succinate indicated no interaction between the drug and starch succinate.

Thus the results of DSC, FTIR and TLC indicated no interaction between the selected drug and starch succinate, the new superdisintegrants. Hence, starch succinate could be used as a superdisintegrant in the design of fast dissolving tablets of the selected drugs.

No visible changes were observed in the fast dissolving tablets after storage. Drug dissolved from the fast dissolving tablets were evaluated before and after storage in each case. No significant difference ($P > 0.05$) was observed in the percent drug content before and after storage for 6 months. The drug release characteristics of the formulation tested remained unaltered during the storage period. The results, thus, indicated that the drug content and drug release rate of the fast dissolving tablets formulated employing starch succinate were quite stable.

Fast dissolving systems is a topic of current interest in pharmaceutical technology. In recent years considerable attention has been focused on the development of or dispersible systems. Such interest is based largely on the fact that the fast dissolving products have established and retained a place in the market based on their uniqueness and their clinical advantages in the practices of medicine. Fast dissolving systems are those formulations designed to release an active ingredient very Fastly in the oral cavity which differ significantly from their corresponding conventional dosage forms. Fast dissolving systems are aimed in enhancing the dissolution rate of poorly soluble drugs and increase their therapeutic activity. Drug release from these systems should be at very fast, reproducible forms play a vital role in the immediate release of the drug from these dosage forms.

In the present investigation starch succinate, a new polymer was prepared and evaluated for its application as super disintegrant in fast dissolving tablet. The specific objectives of the investigation are (i) to prepare and characterize starch succinate, chemical and physical tests and also by X-ray and FTIR spectra. (ii) to evaluate starch succinate as a new super disintegrant polymer for fast dissolving application and (iii) to develop fast dissolving tablets of ibuprofen employing starch succinate and other super disintegrants by wet granulation method.

The starch succinate is a white powder which is crystalline in nature. It is practically insoluble in water, alcohol, petroleum ether and acetone.

For evaluation of starch succinate as a super disintegrant fast dissolving tablets of ibuprofen were prepared employing starch succinate in different proportions in each case by direct compression method. All fast dissolving tablets prepared were evaluated for drug content, hardness, friability, disintegration time and other dissolution characteristics like PD_5, DE_5 and K_1. The dissolution efficiency of starch succinate was compared with that of other super disintegrants commonly used in fast dissolving tablets such as croscarmellose sodium, crospovidone by wet granulation method. Selected best Oro dispersible product formulated employing starch succinate was subjected to accelerated stability testing as per ICH guidelines.

From the results obtained the following conclusions are drawn:

1. All the fast dissolving tablets formulated employing starch succinate were of good quality with regard to drug content, hardness and friability and fulfilled the official (IP/USP) requirements of compressed tablets with regard to the above mentioned physical properties.
2. With ibuprofen drug release from the fast dissolving tablets formulated employing starch succinate (10%) by wet granulation was fast and within 5minutes.
3. Overall starch succinate was found to be a better super disintegrant than as crospovidone, croscarmellose with the ibuprofen and hence it could be used in the formulation of fast dissolving tablets to provide immediate release of the contained drug within 5minutes.
4. Drug release characteristics of the fast dissolving tablets formulated employing starch succinate were quite stable and remained unaltered when subjected to accelerated stability testing at $40^o \pm 2^o$ C and 75% RH for 6 months.

SIGNIFICANT CONTRIBUTIONS AND RECOMMENDATIONS:

The present investigation resulted in the development of starch succinate super disintegrant in fast dissolving tablets for obtaining immediate release of drug. Fast dissolving tablets of ibuprofen formulated employing starch succinate as a super disintegrant exhibited good immediate release characteristics in-vitro and was found suitable for fast dissolving formulations. Hence, starch succinate is recommended as novel super disintegrant in fast dissolving tablets for obtaining immediate release of the poorly soluble drug.

CONCLUSION

Starch succinate is an efficient superdisintegrant for fast dissolving tablets. The disintegration and dissolution efficiency of the fast-dissolving tablets of ibuprofen was good and depended on the concentration of superdisintegrants employed i.e., starch succinate, croscarmellose and crospovidone. The formulated fast dissolving tablets of ibuprofen exhibited good dissolution efficiency in 5min which can be used for the fast therapeutic action of ibuprofen.

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