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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF FLURBIPROFEN

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ABSTRACT

The aim of this research is to formulate and evaluate Flurbiprofen Oral disintegrating Tablets. Flurbiprofen Indicated for the treatment of nonsteroidal anti-inflammatory drugs (NSAIDs). It is primarily indicated as a pre-operative anti-miotic (in an ophthalmic solution) as well as orally for arthritis or dental pain. Hence in this investigation an attempt was made to develop oral disintegrating tablets of Flurbiprofen with super disintegrating agents likeKyron T-314, Poloxomer 188 and Ac-di-Sol. Oral disintegrate tablets were prepared by direct compression method. The tablets were evaluated for the precompression parameters such as bulk density, compressibility, angle of repose etc and post compression parameters like hardness, weight variation, friability, disintegration time, *in-vitro* dissolution studies.*In vitro* dissolution studies The formulation F6 consisting of Poloxomer 188was found be best among all the formulations it has exhibited faster disintegrating time (20 sec) when compared to other formulations and it showed 99.79 % drug release in 30min.

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INTRODUCTION

The oral route of administration isconsidered as the most widely accepted routebecause of its convenience of selfadministration, compactness and easy manufacturing. But the most evidentdrawback of the commonly used oral dosageforms like tablets and capsules is difficulty inswallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients.[1] But it also applies to people whoare ill in bed and to those active workingpatients who are busy or traveling, especiallythose who have no access to water.[2]Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty inswallowing. It has been reported that Dysphagia.[3] (difficulty in swallowing) is common among all age groups and morespecific with pediatric, geriatric populationalong with institutionalized patients ,psychiatricpatients and patients with nausea, vomiting, andmotion sickness complications. ODTs withgood taste and flavor increase the acceptabilityof bitter drugs by various groups of population. This dosage form combines theadvantages of dry and liquid formulation. Somenovel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouthfelling, leaving minimal residue in the mouthafter oral administration. ODT have beeninvestigated for their potential in improvingbioavaibility of poorly soluble drug throughenhancing the dissolution profile of the drugand hepatic metabolism drugs. Orally disintegrating tablets are alsocalled as orodispersible tablets, quickdisintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets,porous tablets, and rapimelts. However, of all the above terms, United Statespharmacopoeia (USP) approved these dosageforms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.[4] United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute.[5]

Drug selection criteria

The ideal characteristics of a drug for oral dispersible tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.

- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT[6]

Desired criteria for ODTs

- ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking technologies should be adopted for bitter taste drugs.
- Exhibit low sensitivity to environment condition such as humidity and temperature.
- ODTs should dissolve / disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug and excipients property should not affect the orally disintegrating tablets.
- Be portable and without fragility concern.[7,8]

Advantages of ODTs

The advantages of ODTs include:

No need of water to swallow the tablet.

- Compatible with taste masking and have a pleasing mouth feel.
- Can be easily administered to paediatric,elderly and mentally disabled patients.
- No residue in the oral cavity afteradministration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipments at minimum cost. Allow high drug loading.
- Accurate dose can be given as comparedto liquids.
- Dissolution and absorption of the drug isfast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation. Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, whichoffers improved bioavailability and thusreduced dose and side effects.
- No risk of suffocation due to physicalobstruction when swallowed, thusoffering improved safety.
- ODTs are suitable for sustained andcontrolled release actives.
- Unit packaging.[9,10]

Limitations of ODTs

It includes

- The tablets commonly have insufficient mechanical strength. Hence, conscientious handling is necessary.
- The tablets may leave an unpalatable taste and grittiness in the oral cavity if not formulated properly.
- Drugs which have large doses, can cause problems to formulate them into ODTs.
- Patients who simultaneously take anticholinergic drugs are not suitable candidates for ODTs.[11,12]

Challenges in the formulation of ODTs

- Mechanical strength and disintegration time: Disintegration time will extend if the mechanical strength is more, so a good cooperation between these two parameters is always necessary.
- Taste masking: Efficient taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.
- Mouth feel: The particles produced after disintegration of the ODT should be very small. ODT should not leave any residue in the mouth after oral administration. Addition of flavors and cooling agents like menthol enhance the mouth feel.
- Sensitivity to environmental conditions: ODTs should have low sensitivity to environmental conditions such as humidity and temperature.
- Cost: The technology adopted for an ODT should be acceptable in terms of cost of the final product.[13,14]

Approaches for Preparation of ODTs: Various preparation techniques have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, taste, swallowability, dissolution profile and bioavailability. Some of those technologies are patented. Basic pharmaceutical processes to manufacture ODTs are explained as follows:

Spray drying: Spray drying methods are used to a great extent in pharmaceutical and biochemical procedures. Spray drying provides a rapid and economically efficient way to eliminate solvents and produces highly porous and fine powders. The formulations are compounded by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, croscarmellose sodium or sodium starch glycolate as disintegrating agent. An acidic material (e.g., citric acid) or alkali material (e.g., sodium bicarbonate) is used to improve disintegration and dissolution behaviour. Tablets prepared by the compression of spray dried powder, when immersed in an aqueous medium, showed a disintegration time of 20 s.[15,16]

Sublimation: Compressed tablet which contains highly water-soluble components can show slo dissolution behaviour, due to the low porosity of the tablets that reduces water penetration into the matrix. By conventional methods, volatile materials are compressed into tablets, these volatile materials can be removed by sublimation, which results in extremely porous structures. The volatile materials which can be used are ammonium carbonate, urea, ammonium bicarbonate, camphor and hexa methylene tetramine. In a few cases, thymol, menthol, camphor, an organic acid such as adipic acid and fatty acid such as arachidic acid, myristic acid, capric acid, and palmitic acid were used as the volatile materials and the sublimation temperature ranged from 40 ºC to 60 ºC. The disintegration time in the oral cavity was found to be about 25 s [17,18].

Freeze drying: Lyophilization process involves removal of solvents from a frozen drug solution or a suspension containing structure-forming excipients. The tablets formed by this process are usually very light and have highly porous structures that allow, rapid dissolution or disintegration. Lyophilization is done at very low temperature to eliminate the adverse thermal effects that may alter drug stability during processing. The freeze dried dosage form have relatively few stability concerns during its shelf life. The drying process may give rise to the glassy amorphous structure of excipients and drug substance.[19,20]

Molding: Molded tablets are made up of watersoluble ingredients. The powder mixture is sprinkled with a solvent (usually water or ethanol). The mixture is molded into tablets under pressure. Applied pressure should be lower than those used in conventional tablet compression. This process is also known as compression molding. Air drying can be used to remove the solvent. Due to lower pressure; a highly porous structure is created, that enhances the dissolution. The powder blend should be passed through a very fine screen, to improve the dissolution rate. Molded tablets disintegrate more rapidly and provide improved taste because of their highly water-soluble, sugar components. However, molded tablets generally do not have high mechanical strength. The chances of breakage of the molded tablets

during tablet handling and opening of blister pockets, is very high. If the hardness enhancing agents are used in the formulation, decrease in disintegration rate is observed. Mechanical strength and good disintegration of the tablets can be improved by using non-conventional equipment and by using multistep processes 21,22.

Mass extrusion: The mass extrusion technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of softened mass through the extruder or syringe is carried out, to get a cylinder of the product which is then cut into even segments using a heated blade to form tablets .[23,24]

Direct compression: Direct compression is the easiest and costeffective tablet manufacturing process. This method can be applied to manufacture ODT by selecting appropriate combinations of excipients, which can provide fast disintegration and optimum physical resistance. Sugar-based excipients are widely used as bulking agents because of their aqueous solubility, sweetness pleasing mouth feel, and good taste masking. Tablets obtained by conventional compression method are less friable, but disintegrate more slowly. The compression method, with or without wet granulation, is a convenient and cost effective way to prepare tablets with sufficient structural integrity .[25,26]

MATERIALS

Flurbiprofen Procured From FDC-Ltd (Roha Maharashtra, India). Provided by SURA LABS, Dilsukhnagar, Hyderabad. Kyron T-314S.D. Fine chemicals, Mumbai, India, Poloxomer 188Rubicon Research Pvt. Ltd., Mumbai, India, Ac-di-SolMerck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Buffer preparation

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.128 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2 M potassium dihydrogen orthophosphate and 112.5 mL of 0.2 M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method development forFlurbiprofen:

Determination of absorption maxima: A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 225nm. Hence all further investigations were carried out at the same wavelength.

Construction of standard graph: 100 mg of Flurbiprofen was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (100µg/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2, 4, 6, 8 and 10 µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 225nm.

Formulation development

Drug and different concentrations of super disintegrants (Kyron T-314, Poloxomer 188 and Ac-di-Sol)and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.

- The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 min.

Table 1. Formulation table showing various compositions

Ingredients (MG)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flurbiprofen	50	50	50	50	50	50	50	50	50
Kyron T-314	20	40	60	-	-	-	-	-	-
Poloxomer 188	-	-	-	20	40	60	-	-	-
Ac-di-Sol	-	-	-	-	-	-	20	40	60
Aspartame	15	15	15	15	15	15	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	6	6	6	6	6	6	6	6	6
MCC	104	84	64	104	84	64	104	84	64
Total Weight (mg)	200	200	200	200	200	200	200	200	200

All the quantities were in mg

Table 2. Calibration curve data of Flurbiprofen in pH 6.8 phosphate buffer

Concentration	Absorbance
0	0
2	0.122
4	0.216
6	0.341
8	0.452
10	0.568

- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

RESULTS AND DISCUSSION

Preparation of calibration curve of Flurbiprofen

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of y=0.056 x-0.000. Hence Beer-Lambert's law was obeyed.

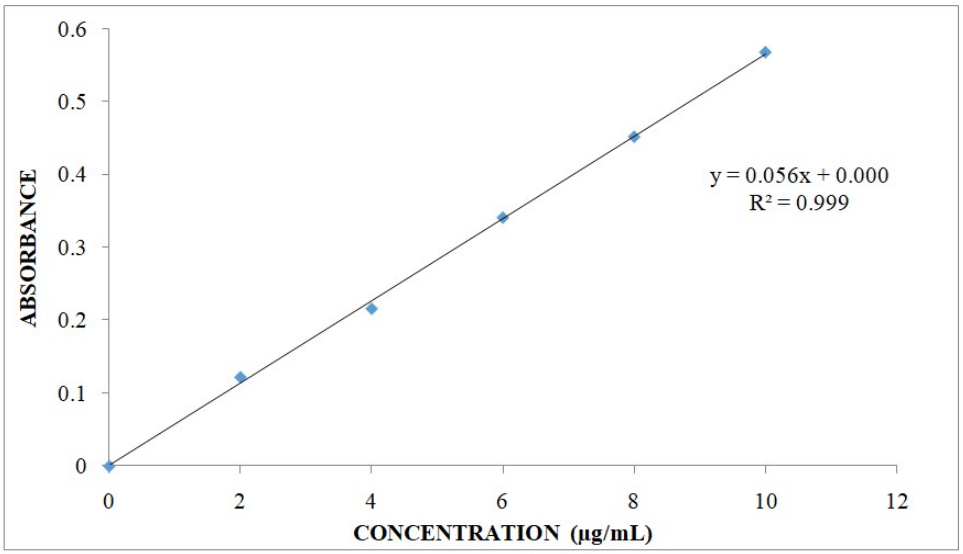

Fig. 1. Calibration curve data of Flurbiprofen in pH 6.8 phosphate buffer

Evaluation of pre-compresion parameters of powder blend

Table 3. Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density(gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio
F1	25.01	0. 59	0.57	14.03	1.16
F2	26.8	0. 46	0.67	16.41	1.19
F3	27.7	0. 32	0. 54	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	25.24	0.52	0.65	18.46	1.22
F6	28.12	0. 46	0. 56	15.15	1.17
F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.67	15.78	1.18
F9	26.45	0.54	0.65	16.92	1.25

✓ The bulk density of all formulations was found in the range of 0.32 - 0.59 and tapped density was in the range of 0.54 - 0.67 The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

Evaluations of Post Compression Parameters of Flurbiprofen Odts

Table 4. Evaluation of post compression parameters of Flurbiprofen Oral disintegrating tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration Time (sec)
F1	198.69	3.9	0.35	4.15	98.27	42
F2	200.14	3.2	0.62	4.62	100.05	38
F3	197.60	4.2	0.43	4.82	99.57	30
F4	200.28	3.9	0.52	4.92	96.42	37
F5	199.37	4.3	0.60	4.71	99.10	31
F6	196.81	3.8	0.72	4.65	97.35	20
F7	198.59	3.7	0.49	4.12	98.41	35
F8	199.84	4.3	0.39	4.80	99.89	31
F9	197.62	3.6	0.43	4.17	97.38	26

***In vitro* drug release studies of Flurbiprofen**

Table 5. Dissolution data of Flurbiprofen

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	20.82	25.40	31.42	28.15	33.07	41.46	17.90	23.92	20.13
10	35.19	46.68	50.21	48.98	50.36	52.20	38.45	36.53	40.31
15	51.24	53.25	57.78	66.41	69.04	71. 31	46.14	44.79	49.96
20	59.63	62.12	76.01	75.82	78.12	82.19	60.54	58.12	63.59
25	67.10	80.55	85.95	80.15	82.75	91.96	65.16	65.74	75.98
30	79.09	86.36	97.61	87.76	92.33	99.79	78.50	81.10	96.49

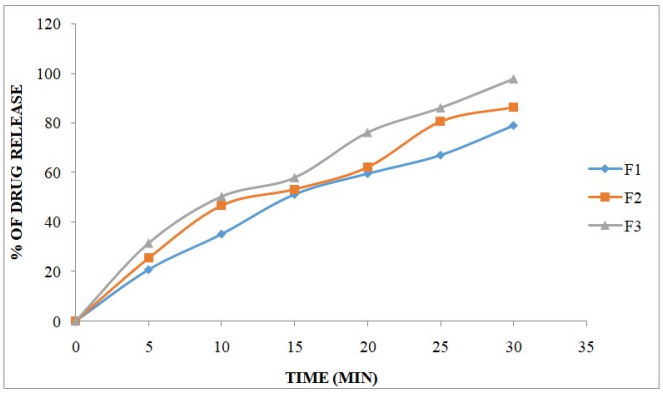

Fig. 2. Dissolution profile of formulations F1, F2, F3

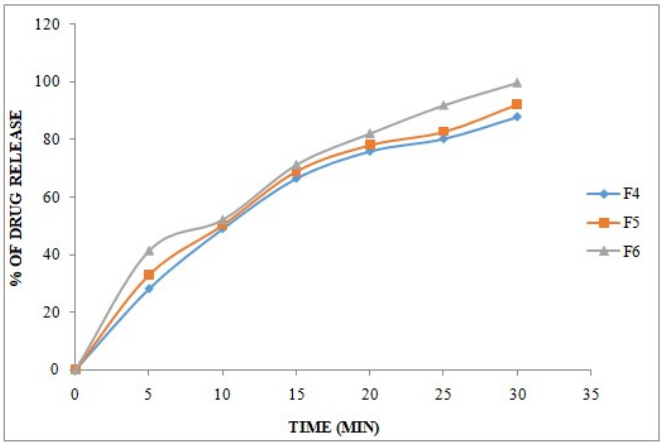

Fig. 3. Dissolution profile of formulations F4, F5, F6

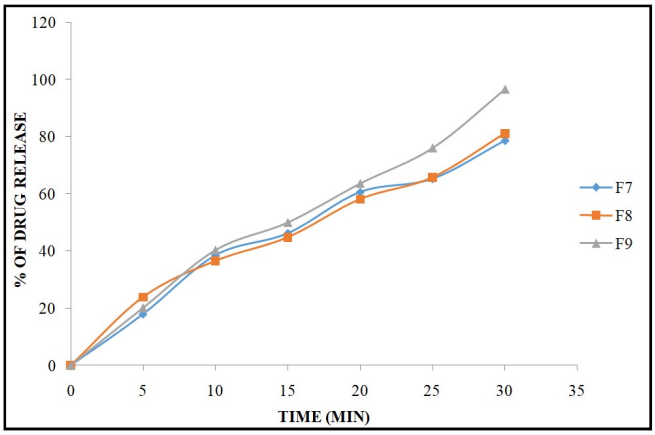

Fig. 4. Dissolution profile of formulations F7, F8, F9

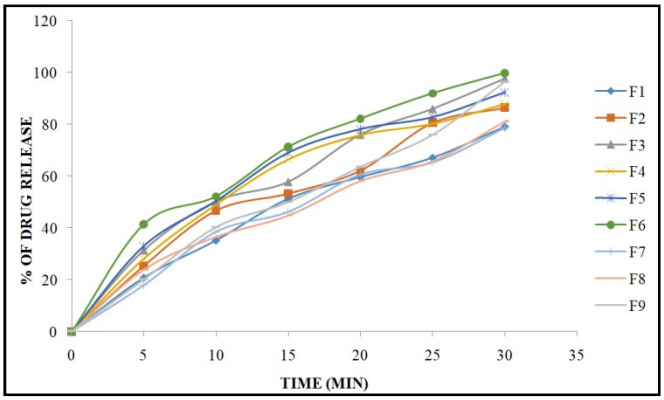

Fig. 5. Dissolution profile of all formulations F1-F9

Ftir results

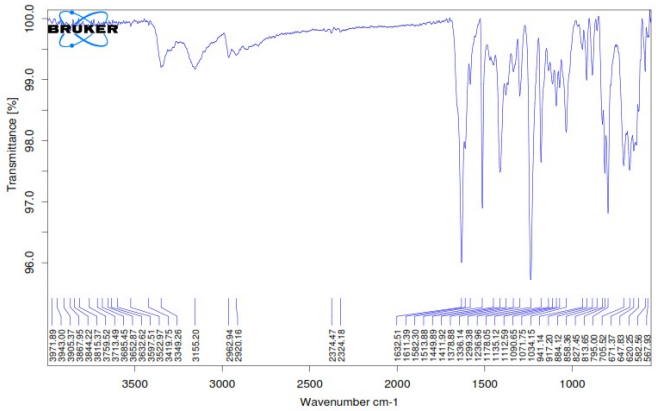

Fig. 6. FTIR of Flurbiprofen Pure Drug

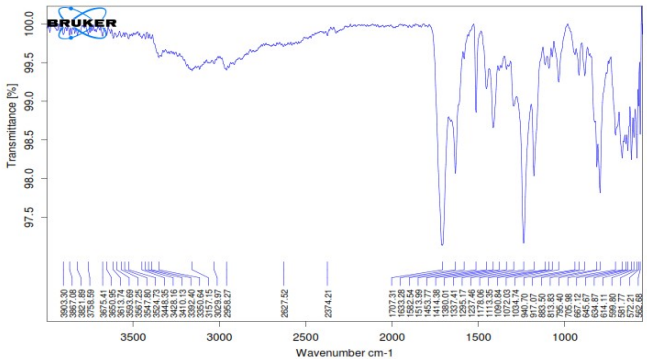

Fig. 7. FTIR of Flurbiprofen optimized formulation

Flurbiprofen was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions.

CONCLUSION

Oral disintegrating tablets of Flurbiprofen were developed by using different disintegrants to avert the problem of swallowing and provide rapid onset of action, which improves patient compliance and quality of life. FTIR study reveals that there is no drug-excipients interaction between Flurbiprofen and excipients. The blend of all 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. The F6 formulation was showed good drug release than the other formulations. The F6 formulation was released 99.79% and consider as an optimized. The developed formulation of Flurbiprofen showed good efficacy, rapid onset of action, better patient compliance.

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