Flurbiprofen: β-cyclodextrin formulations: an improved method for fast dissolving tablet

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ABSTRACT

The goal of the present investigation was to design and evaluated taste mask of fast dissolving tablet of Flurbiprofen, by addition of super-disintegrant method using various excipients ,Ac-di-sol, Avicel, Manitol and β-Cyclodextrin (β-CD).Flurbiprofen is an anti-inflammatory and analgesic drug used in the treatment of chronic rheumatoid diseases which is a painful condition and therefore requires drugs that has rapid onset of action The feasibility of formulating the β-cyclodextrin complexes of Flurbiprofen (1:3) into tablet dosage forms is evaluated. Solid inclusion complexes of Flurbiprofen prepared by kneading method were formulated into tablets by direct compression methods. All the tablets formulated employing β-cyclodextrin complexes of Flurbiprofen gave rapid and higher dissolution rates of when compared to that of Flurbiprofen plain tablets. The prepared formulations were evaluated for hardness, friability, and disintegration time, wetting time, drug content and in-vitro drug release studies. Fast dissolving tablet prepared by addition of super-disintegrant method with Ac-di sol (4-8%) showed 99.85% in 12 minute. On the various data obtained showed that the use of super-disintegrants to formulate fast dissolving tablets of Flurbiprofen was a good way to enhance bioavailability, dissolution rate and absorption rate of the drug.

KEY WORDS: β-Cyclodextrin, Ac-di sol, SSG, Kneading Method, direct compression.

1. INTRODUCTION

The concept of Mouth Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Dysphagia or difficulty in swallowing is common among all age groups. Dysphagia is common in about 35% of the general population, well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and paediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. Flurbiprofen is a member of the phenylalkanoic acid derivative family of non-steroidal anti-inflammatory drugs (NSAIDs) used to treat the inflammation and pain of arthritis. Flurbiprofen is also used as an active ingredient in some kinds of throat lozenges (Strepsils Intensive) Chemically it is (*RS*)-2-(2-fluorobiphenyl-4-yl) propanoic acid.

Flurbiprofen as a phenylalkanoic acid derivative which belonged to a group of poorly water soluble drugs and classified as a non-steroidal anti-inflammatory drug whose major indication is in the long-term treatment of chronic rheumatoid diseases. Flurbiprofen being a class II drug is therefore limited in its therapeutic activity due to its slow rate of absorption from the oral route of administration. The poor dissolution of relatively insoluble drugs has a major pharmacokinetic problem in the oral dosage form. This limits aspects such as absorption and bioavailability. Therefore several approaches have been followed in improving the solubility of drugs, on being complexation using β-cyclodextrin. Amongst the existing β-Cyclodextrin (β-CD) has been used extensively to modify their physico-chemical properties. In the treatment of osteoarthritis, rheumatoid arthritis, acute gouty arthritis and ankylosing spondylitis, therapeutic doses of flurbiprofen have proven to be as effective as the other commonly used NSAIDs

The basic approach in development of fast dissolving tablets is the use of superdisintegrants like Cross linked Ac-di-sol, Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. Super disintegrants provide fast disintegration due to collective effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The objective of the present study is to enhance the dissolution rate of Flurbiprofen tablets using superdisintegrants. Flurbiprofen is selected as the model drug which comes under Non-steroidal anti-inflammatory drug (NSAIDs) class. Flurbiprofen is a member of the phenylalkanoic acid derivative family of NSAIDs,

which are widely used for the long-term treatment of chronic rheumatic diseases such as rheumatoid arthritis, osteoarthritis and alkylosing spondylitis. It is effective in inhibiting surgically induced miosis in human eyes while cataract extraction.

Preparation of Cyclodextrin complexes: β-Cyclodextrins act as dissolution enhancers because it consist truncated cone type structure. The outer surface is hydrophilic due to the presence of hydroxyl groups and the interior of the cone is hydrophobic due to presence of glycosidic ether oxygen at O-4 and the hydrogen attached to C-3 and C-5 and thereby provides a lipophillic microenvironment into which drug can enter and can be partially or fully included without covalent bonding, while outer hydrophilic environment contributes to drug dissolution.

Solid complexes of Flubiprofen and β-cyclodextrin, were prepared in 1:3 ratio employing kneading method. The natural cyclodextrins, in particular β-cyclodextrin, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these cyclodextrin can be of limited solubility resulting in precipitation of solid cyclodextrin complexes from water and other aqueous systems. In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state. Substitution of any of the hydrogen bond forming hydroxyl groups, even by lipophilic methoxy functions, results in dramatic improvement in their aqueous solubility.

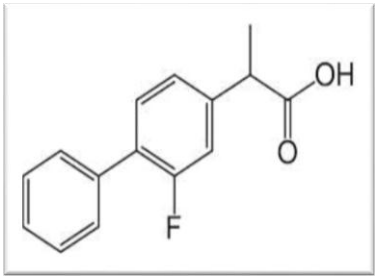

Figure.1.Structure of Flubiprofen

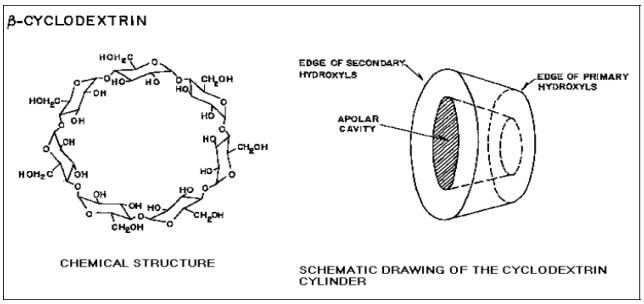

Figure. 2. The chemical structure and the molecular shape of β-cyclodextrin (βCD)

2. MATERIALS AND METHODS

Kneading Method: Flubiprofen and β-cyclodextrin, were triturated in a mortar with a small volume of a solvent blend of water-methanol (3:2). The thick slurry was kneaded for 45 min and then dried at 55^{O} C until dry. The dried mass was pulverized[7] and sieved through mesh No.120.

Formulation of mouth dissolving tablets of flurbiprofen:

Super disintegrants addition method: Specified quantity of flubiprofen, Avicel (20%), Ac-di-sol(2-5%), Sodium Starch glycolate (2-8%), aspartame(0.4%), mannitol, and magnesium stearate were weighed accurately and passed through 60 #screen.

All the materials were transferred to mortar and tri turated till it mixed uniformly. The resulting powder mixture was compressed into tablets using single punch tablet machine.

Table.1.Composition of flubiprofen fast dissolving tablet (in mgs)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flubiprofen:β-cyclodexyrin Complex (mg)	200	200	200	200	200	200	200	200	200
Avicel	100	100	100	100	100	100	100	100	100
Ac-di-sol	12	15	20	12	15	20	12	15	20
SSG	10	10	10	20	20	20	30	30	30
Aspartame	10	10	10	10	10	10	10	10	10
Menthol	2	2	2	2	2	2	2	2	2
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Mannitol q.s.	500	500	500	500	500	500	500	500	500

Table.2.Physical properties of powder blend

Formulations	Angle of Repose (°) ±SD	Bulk Density (g/ml) ±SD	Tapped Densi-ty(g/m) ±SD	Carr's Index (%)±SD	Hausner's Ratio ±SD
F1	27.90±0.30	0.42±0.035	0.59±0.055	12.87±0.56	1.50±0.006
F2	24.62±0.50	0.40±0.015	0.62±0.019	12.72±0.30	1.49±0.002
F3	27.60±0.40	0.41±0.025	0.68±0.022	11.71±0.65	1.12±0.008
F4	26.30±0.79	0.40±0.029	0.69±0.050	15.45±0.89	1.19±0.013
F5	25.69±0.59	0.43±0.035	0.70±0.035	13.79±0.85	1.55±0.012
F6	26.89±0.56	0.42±0.035	0.68±0.039	12.85±0.44	1.54±0.018
F7	27.90±0.39	0.39±0.033	0.65±0.032	11.39±0.28	1.52±0.006
F8	26.99±0.22	0.44±0.025	0.67±0.035	13.60±0.82	1.42±0.015
F9	28.54±0.30	0.43±0.036	0.65±0.055	14.44±0.98	1.50±0.011

***In Vitro* Dissolution Testing:** Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab, Mumbai, India.). The dissolution test was per formed using 900ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. Ten ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 247nm. In Vitro Dissolution Testing Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab, Mumbai, India.). The dissolution test was per USP.

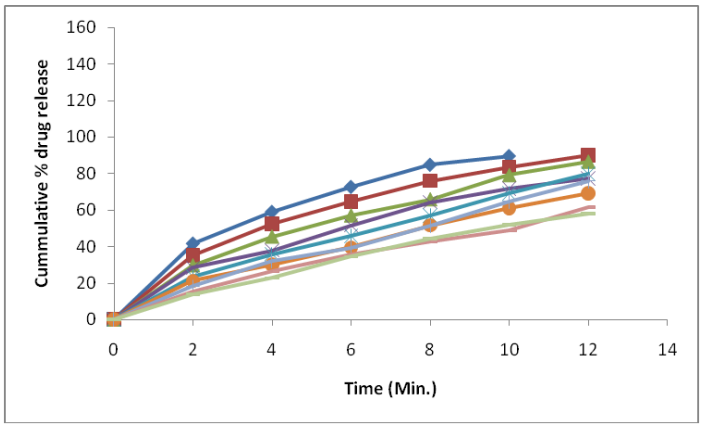

Figure.3.*In vitro* drug release profile of FDTs of flurbiprofen in 6.8 pH Buffer

Table.3.Physical parameters of fast dissolving tablet of Flurbiprofen

Formulations	Thickness (mm)±SD	Hardness (kg/cm2)±SD	Weight Variation (mg)±SD	% Friability ± SD	Wetting time (Sec) Mean±SD	Water absorption ratio Mean±SD	Disintegration time (Sec) Mean±SD	Content uniformity Mean(%)± SD
F1	4.82±0.039	3.36±0.11	303.55±0.30	0.55±0.19	39.22±0.22	92.78±0.58	45.15±0.67	99.25±0.59
F2	4.59±0.040	3.44±0.44	303.60±0.55	0.59±0.16	37.55±0.12	94.29±0.88	58.18±0.44	96.89±0.36
F3	4.88±0.050	3.49±0.36	301.58±0.60	0.51±0.22	35.45±0.20	95.32±0.78	46.58±0.20	99.88±0.29
F4	4.88±0.056	3.55±0.10	302.45±0.25	0.57±0.12	38.85±0.44	98.65±0.44	52.20±0.54	98.80±0.25
F5	5.05±0.045	3.45±0.55	300.55±0.22	0.58±0.17	35.70±0.35	94.36±0.75	46.88±0.88	97.88±0.25
F6	4.99±0.048	3.44±0.32	301.48±0.36	0.59±0.14	36.61±0.50	98.00±0.05	56.55±0.40	98.97±0.80
F7	4.99±0.056	3.55±0.26	300.59±0.10	0.58±0.158	35.22±0.55	94.91±0.55	49.52±0.80	96.99±0.45
F8	4.59±0.059	3.58±0.04	302.54±0.23	0.61±0.29	38.98±0.50	95.69±0.55	51.60±0.75	98.60±0.20
F9	4.47±0.042	3.38 ±0.19	301.58±0.31	0.67±0.11	37.12±0.27	92.65±0.82	57.60±0.60	99.60±0.60

Characterization of flurbiprofen tablet:

FT-IR studies: Infrared spectrum was taken for the pure flurbiprofen. FT-IR studies was carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy (FTIR) (Shimadzu).

3. RESULTS AND DISCUSSION

Flubiprofen is bitter in test. So first of all it was taste masking by β-cyclodextrin. Solid complexes of Flubiprofen and β-cyclodextrin, were prepared in 1:3 ratio employing kneading method when guest molecules are incorporated in the -cyclodextrin cavity or in the crystal lattice, their melting, boiling, and sublimation points usually are shifted to a different temperature or disappear within the temperature range in which the ß-cyclodextrin lattice is decomposed.

Therefore β-cyclodextrin successfully taste masking the flurbiprofen drug The different batches of flurbiprofen fast issolving tablets were prepared by direct compression method *flurbiprofen* fast dissolving tablets were prepared by direct compression method was carried out by using uperdisintegrants like Ac-di-sol(2-5%), Sodium Starch glycolate (2-8%), concentration. Angle of repose: range from 24.62±0.50° to 28.54±0.30° show good flow. Bulk density and tapped density: range from 0.39±0.033 to 0.44±0.025 (g/ml), and 0.59±0.055 to 0.70±0.035 (g/ml), respectively. Compressibility index and Hausner ratio find out range from 11.39±0.28to 15.45±0.89and 1.12±0.008 to 1.55±0.012 respectively. The results for recompressed parameters are showed in Table 2. Disintegration time: at various storage conditions increases but less than 1min. In this studies weight variation test range from 300.55±0.22 mg to 303.60±0.55 mg as per USP specification. Friability: less than 0.59±0.16 % the results indicate that the percentage losses were not more than 1.0%. So the tablet complies as per USP specifications. Thickness: range from 4.59±0.040 to 5.05±0.045mm; the results indicate that the tablets are suitable for packing. Content uniformity: was found in between 96.89±0.36 % to 99.88±0.29 %. Hardness of tablet was found to be between 3.44±0.32 to 3.55±0.26 kg/cm2. The results indicate that the tablets are mechanically strong and are in limit. Disintegration time: in between 45.15±0.67 to 58.88±0.88 second the results indicate that disintegration time of tablets is within 1minute. Wetting time: in between 39.22±0.22 to 39.12±0.27 seconds and water absorption ratio was found to be 92.78±0.58 to 99.32±0.78.

The post compressed parameters are showed in Table 3. Dissolution Study in 6.8 pH phosphate buffer: formulation of F1, F2, F3, F4, ,F5 F6, F7, F8,and F9 have a recorded drug release 94.84%, 96.81%, 98.07%, 92.85%, and 99.48% , 97.88%, 96.43%, 98.80%, 96.97%, and 95.23% at the end of 12 min. Dissolution studies shows there was no significant difference in dissolution data of formula-tions at initial and after specified storage period.

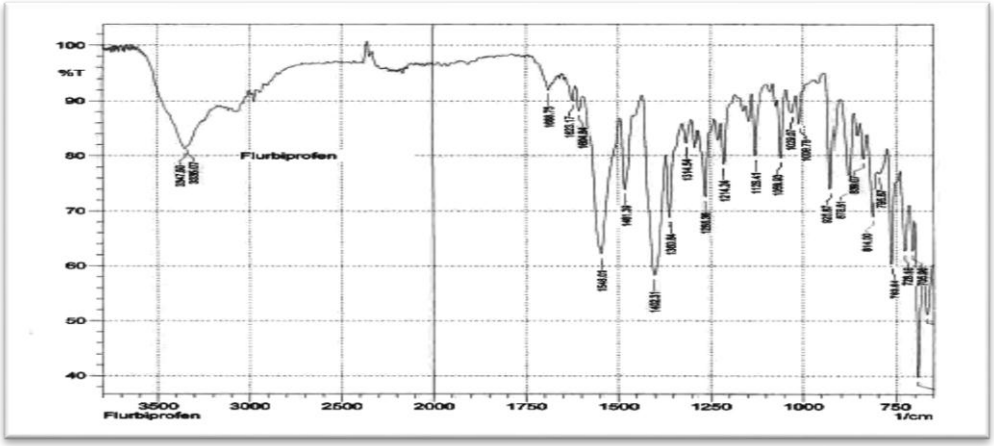

Figure.4.FTIR Spectra of test sample of flurbiprofen pure drug

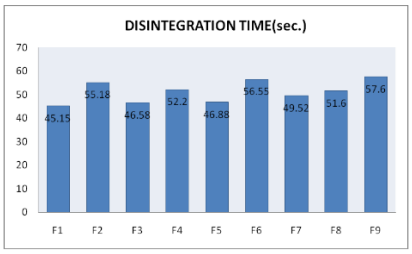

Figure.5.Disintegration time of various formulations of FDT of Flurbiuprofen

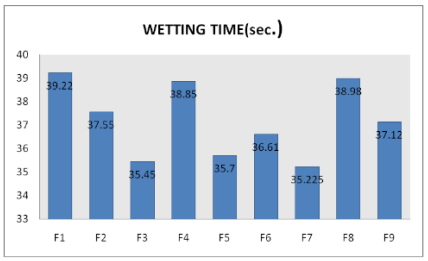

Figure.6.Wetting time of various formulations of FDT of Flurbiuprofen

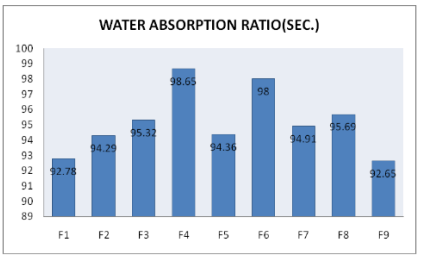

Figure.7.Water absorption ratio of various formulations of FDT of Flurbiuprofen

4. CONCLUSION

It may be concluded complex of flurbiprofen with β-cyclodextrin(1:3) prepared by Kneading Method. In these studies further formulation of Fast dissolving tablets of poorly soluble drug flurbiprofen with β-cyclodextrin complex by direct compression with the use of superdisintegrant like Ac-di- sol and SSG. And Formulation F5 showed better result as compared to market tablet.

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