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Formulation and Evaluation of Orodispersible Tablets for Kids.

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ABSTRACT
The present research was aimed to prepare orodispersible tablets for kids using model drug cefixime. Orodispersible tablets were prepared using different concentration of superdisintegrant addition method by direct compression technique. Tablets were evaluated for various evaluation parameter likes drug content, weight variation, friability, hardness, wetting time and invitro disintegration time. Evaluation results for all batch of formulation showed obey of pharmaceutical standards. Batch F3 showed shortest in-vitro disintegration time and fast drug release. From the study it was concluded that use of superdisintegrant addition method was observed to be good choice for preparation of Orodispersible tablets of cefixime for kids.
Keywords: *Cefixime, Orodispersible tablets, Kids, Superdisintegrant etc.*

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I. INTRODUCTION

The oral route is the most convenient and commonly accepted method of drug administration. It doesn't require special equipment or healthcare professionals, making it accessible and easy for patients to self-administer medications at home. This convenience often leads to better patient compliance with prescribed treatment regimens, ultimately improving therapeutic outcomes. The oral route offers versatility in drug formulation, allowing for a wide range of dosage forms such as tablets, capsules, powders, suspensions, and solutions. Many drugs are well absorbed through the gastrointestinal tract, allowing for rapid onset of action and predictable pharmacokinetics.[1,2]

Orodispersible tablets represent a versatile and patient-friendly dosage form that has gained significant popularity in the pharmaceutical industry. These tablets are designed to disperse rapidly in water or other liquids, forming a uniform suspension or solution, thus offering a convenient alternative for individuals who have difficulty swallowing solid dosage forms like conventional tablets or capsules. The orodispersible tablets has addressed various challenges associated with medication administration, particularly for certain patient populations such as kids. By providing a kids friendly and palatable option, orodispersible tablets enhance patient compliance. The formulation of orodispersible tablets typically involves the use of water-soluble excipients and disintegrants, which promote rapid dispersion upon contact with liquid. These tablets often incorporate superdisintegrants to facilitate quick disintegration and dissolution, ensuring rapid onset of action and optimal drug delivery. Orodispersible tablets with tasted masked or sweet taste often used to increase the patient's acceptance like kids. Cefixime is a broad-spectrum, third-generation cephalosporin antibiotic used primarily in the treatment of bacterial infections. Hence the present work was aimed to formulate Orodispersible tablets of cefixime for kids using different superdisintegrant.[3,5]

II. MATERIALS AND METHODS

Materials.

Cefixime was received as a gift sample from Ajanata Pharma, Mumbai, India. Croscarmellose sodium, Sodium starch glycolate and Low substituted hydroxypropyl cellulose (LHPC) was obtained as gift sample from Signet Chemicals Mumbai. All other materials like aspartame, mannitol, Avicel 102, magnesium stearate, talc used was of analytical grade and procured from commercial sources.

Methods

Formulation of Orodispersible tablets:

Orodispersible tablets of cefixime was prepared by superdisintegrant addition method using direct compression technique. The various super disintegratants like croscarmellose sodium, sodium starch glycolate

and low substituted hydroxypropyl cellulose were utilized in different concentration for the tablets preparation. Aspartame was used as sweetener, while Avicel pH 102 was used as filler. Before formulation all the ingredients were passed through sieve number 40. Required quantity of each ingredient was taken for each specified formulation, and all the ingredients were co ground in a mortar and pestle. 1% magnesium stearate and 1% talc were then blended with the initial mixture. The resulting powder mixture was compressed into tablet with 8 mm flat-face punches using rotary tablet punching machine. (Chamunda Press). The details for the formulation of orodispersible tablets was shown in table 1.[5,7]

Table. 1: Composition of Orodispersible Tablets of Cefixime

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime	100	100	100	100	100	100	100	100	100
Croscarmellose Sodium	4	6	8	-	-	-	-	-	-
L-HPC	-	-	-	4	6	8	-	-	-
Sodium Strach Glycolate	-	-	-	-	-	-	4	6	8
Aspartame	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2	2
Avicel 102	90	88	86	90	88	86	90	88	86
Total Weight	200	200	200	200	200	200	200	200	200

EVALUATION OF POWDER BLEND

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml.

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for multiple times and the tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml.

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\tan(\theta) = h / r$

$\theta = \tan^{-1}(h / r)$

Where, θ is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

Carr's Index Or % Compressibility

The Carr's compressibility index, also known as the Carr index or Carr's index, is a parameter used to assess the compressibility and flow properties of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the bulk density and tapped density of the powder and provides insights into its flowability and compaction characteristics. It indicates powder flow properties.

Hausner Ratio

Hausner's ratio, is a parameter used to assess the flowability of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the tapped density and bulk density of the powder and provides insights into its flow properties. The Hausner ratio is defined as the ratio of tapped density to bulk density. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). [8-9]

EVALUATION OF ORODISPERSIBLE TABLETS

Weight Variation

The weight variation test is a pharmaceutical quality control test performed on tablets and capsules to ensure uniformity of dosage units within a batch or lot. It is a critical test to verify that each tablet or capsule contains the specified amount of active pharmaceutical ingredient (API) and excipients, as stated on the product label.

This ensures consistent dosing and therapeutic efficacy for patients consuming the medication. 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The average weight per unit is then calculated by dividing the total weight by the number of units in the sample.

Hardness and Thickness

Tablet hardness, often measured in terms of breaking force or resistance to crushing, provides an indication of the mechanical strength and robustness of the tablet. Hardness testing ensures that tablets can withstand handling, packaging, and transportation without breaking or crumbling, thereby maintaining their integrity and appearance throughout their shelf life. Hardness or tablet crushing strength ie the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Tablet thickness is directly related to the amount of material compressed into each tablet during the manufacturing process. Consistent tablet thickness across a batch ensures uniformity in drug content and dosage within each tablet. The thickness of the prepared tablets was measured using vernier caliper. It is expressed in mm.

Friability (F):

The friability test is a important quality control measure in pharmaceutical manufacturing, primarily for solid oral dosage forms such as tablets. It assesses the mechanical strength and resistance to abrasion of tablets during handling, packaging, and transportation. The friability test ensures that tablets maintain their physical integrity and withstand mechanical stress under normal handling conditions. Friability of the tablet was determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed and the friability (F) was calculated.

In-Vitro Disintegration Time

The in-vitro disintegration time was determined using USP disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds/minute taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured and recorded. [10-11]

Wetting Time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. Wetting time of tablets was determined using a piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. [12,13]

Content Uniformity

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and quantity of powder equivalent to 100 mg of drug was taken and transfer it to 10 ml of 6.8 pH phosphate buffer. The resulting solution was then diluted appropriately and measured using a UV-Visible spectrophotometer at 288 nm. [14]

In-Vitro Dissolution Study

The in-vitro dissolution study was carried out in USP dissolution test apparatus type II (paddle) with a dissolution medium of 900 ml of phosphate buffer pH 6.8, at 50 rpm (37±0.5°C). 5 ml aliquot was withdrawn at the specified time interval, filtered through whatman filter paper, and measured spectrophotometrically after suitable dilution at 288 nm using UV-Visible spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37°C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The results in the form of percent cumulative drug released was calculated. [15,16]

Comparative Study of Optimized Formulation with Standard Marketed Formulation

Comparative dissolution profile between standard marketed cefixime orodispersible kids tablets formulation (Hifen100 DT, Hetero Drugs Ltd) and optimized cefixime kids tablets formulation (F3) was performed. Comparative study was performed in dissolution test device II (paddle design). Phosphate buffer pH 6.8 (900 ml) was used as dissolution medium which was adjusted at 37±0.5°C throughout study. Speed of

device was maintained at 50 rpm. To keep the sink condition, 5 ml samples were taken at pretended time slot. The amount of sample withdrawn was supplanted with similar media in the same volume. Using a UV-visible spectrophotometer, collected samples were examined at 288 nm after appropriate dilution. [17]

Stability study

A stability study is a systematic investigation conducted to assess the chemical, physical, and microbiological stability of pharmaceutical products under various environmental conditions over time. The primary purpose of stability studies is to determine how the quality attributes of a pharmaceutical product change over time under different storage conditions, such as temperature, humidity, light exposure, and packaging materials. The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40ºC and 75% RH for the period of 3 months. The Tablet were evaluated before and after 3 months for change in appearance, Hardness, disintegration time, drug content and In vitro drug release.[18-19]

III. RESULTS AND DISCUSSION

Orodispersible kids tablets containing Cefixime were prepared by using Croscarmellose Sodium, sodium starch glycolate and L-HPC as a superdisintegrants (Table 1). Nine batches were prepared by direct compression technique using different concentration of superdisintegrant. IR spectroscopy study shown the compatibility between drug and excipient. The pre-compression parameters for all batched were evaluated and found within prescribed limit and showed good free flowing property (Table 2). All parameters like bulk density, tapped density, hausner ratio, percentage compressibility and angle of repose were found within acceptable limit of standards. Results were shown in table 2.

Table 2. - Micromeritic properties of power blend

Batch	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	27.60	0.167	0.181	7.73	1.08
F2	28.61	0.160	0.173	7.51	1.08
F3	26.16	0.167	0.182	8.24	1.09
F4	29.74	0.169	0.200	15.50	1.18
F5	28.32	0.159	0.182	12.64	1.14
F6	29.28	0.180	0.201	10.45	1.12
F7	29.46	0.171	0.203	15.76	1.19
F8	28.67	0.178	0.198	10.10	1.11
F9	30.12	0.165	0.195	15.38	1.18

The prepared tablets were subjected to post-compression parameters likes hardness, friability, weight variation, amount of drug content, in-vitro wetting time and in-vitro disintegration time. The hardness for all the batch formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulation the friability values are less than 1%. All the tablets passed weight variation test. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, disintegrants and excipients. The percentages drug contents of all the tablets batch were found in the range of 97.24 to 99.71% which ware in pharmacopoeial limits. The thickness of all batch was found from the range of 2.90 to 3.21 mm for formulation F1 to F9 is found to be optimum and indicated well distribution of pure drug.

Formulation F1, F2 and F3 prepared with crosscarmillose sodium as superdisintegrant at concentration of 2%, 3% and 4% of total tablets weight was found as 42.32 ±3.53, 32.10 ±4.10 and 20.36±2.62 respectively Batch F3 showed least disintegration time of 20.36 sec as compare to F1 and F2. Formulations batch F4, F5 and F6 prepared with L-HPC as superdisintegrant at concentration of 2%, 3% and 4% was found as 46.34±3.42, 38.56±4.25 and 32.62±3.12 sec respectively, while disintegration time for formulations F7, F8 and F9 prepared with sodium starch glycolate as superdisintegranat at similar concentration was found as 53.37±4.46, 37.55±3.50 and 34.23±4.58 sec respectively. From the study it was observed that as the concentration of superdisintegrant increases, the disintegration time decreases. This observation was seen in all formulation. This might be due to higher concentration and wicking action of super disintegrating agent. Among all the formulation batch F3 showed lowest disintegration time (20.36 sec) as compare with other formulations. (figure 1)

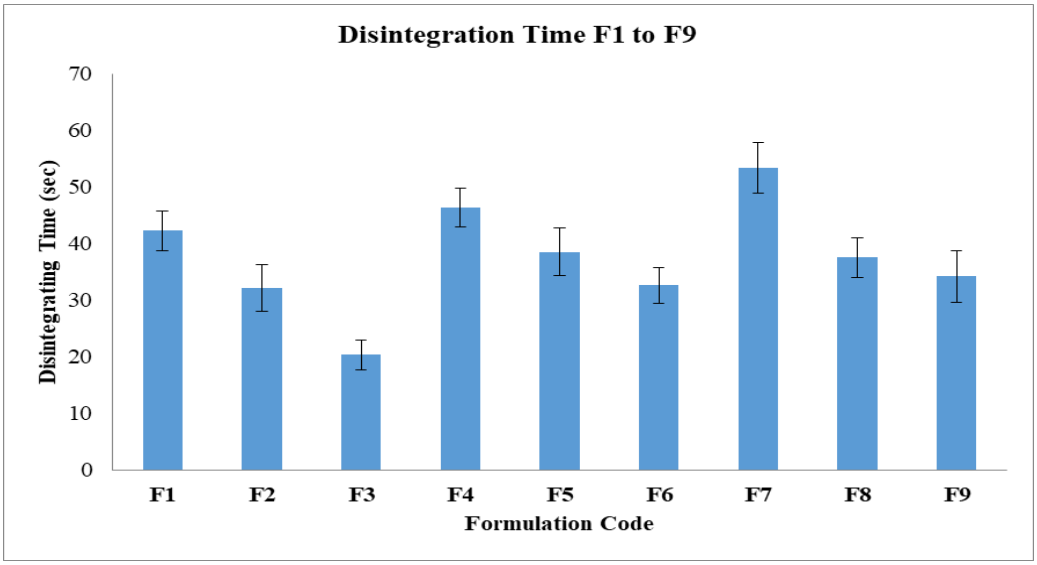

Figure 1: Disintegrating time of formulation F1 to F9

The wetting time for formulation F1 to F9 was found to be in range of 32.4 to 65.8 sec. Weeting time for tablets was observed to be decreases with increase in concentration of superdisintegrant, this might be due to wicking action of superdisintegrating agent. All batch formulation showed lower weeting time. Tablets prepared with Croscarmellose sodium showed lowest weeting time as compare to LHPC and Sodium starch glycolate, this may be due to higher wicking power of Croscarmellose sodium. The the post compression parameters were shown in table 3.

Table 3. – Post Compression parameters of Orodispersible Tablets of Cefixime

Batch	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/Cm^2)	Friability (%)	Drug Content Uniformity (%)	Disintegration Time (sec)	Wetting Time (Sec)
F1	Passed	3.10±0.05	4.5±0.60	0.71±1.1	97.74±1.1	42.32 ±3.53	50.8 ±1.07
F2	Passed	2.96±0.07	4.5±0.55	0.68±0.9	97.82±1.2	32.10 ±4.10	34.0 ±0.95
F3	Passed	3.10±0.07	5.0±1.30	0.64±0.12	99.30±1.1	20.36±2.62	28.4 ±1.65
F4	Passed	3.21±1.8	4.5±0.80	0.82±0.18	98.04±1.1	46.34±3.42	54.0 ±1.85
F5	Passed	2.90±1.2	5.0±0.58	0.77±0.27	97.24±1.3	38.56±4.25	41.0 ±2.35
F6	Passed	3.12±1.2	4.5±0.85	0.66±0.16	98.26±0.4	32.62±3.12	38.4 ±1.480
F7	Passed	2.98±1.3	4.5±1.26	0.82±0.31	99.71±1.0	53.37±4.46	56.8 ±0.35
F8	Passed	3.10±1.4	4.5±1.16	0.80±0.24	98.40±0.9	37.55±3.50	40.7 ±1.45
F9	Passed	2.96±1.5	5.0±1.12	0.78±0.23	97.82±1.8	34.23±4.58	32.1 ±1.05

***** All values are expressed as mean ± SD, n=3

In-Vitro Dissolution Study

In vitro drug release study of prepared orodispersible tablets of cefixime was determined in phosphate buffer pH 6.8. Formulations F1, F2 and F3 prepared with 2 croscarmellose sodium showed 98.18 ±1.67, 98.84 ±2.78 and 101.2 ±1.05% drug release respectively in 30 min. Formulation F4, F5, and F6 prepared with LHPC showed 96.30 ±1.65%, 98.62 ±1.54% and 98.74±2.60 % drug release respectively in 60 min. While formulation F7, F8 and F9 prepared with 2%, 3% and 4% of sodium starch glycolate showed drug release of 97.26±3.23%,

97.22±2.40% and 99.05±2.10% drug release at the end of 60 min. All the formulation showed rapid drug release because of presence of super disintegrating agent, meeting the criteria of Orodispersible tablets. All batch formulation showed more than 70% drug release in first 10 min time interval.

Among the formulation batch F3 prepared with 4% of croscarmellose sodium showed fastest drug release ie almost 96.4% in just 10 min time, which was highest among the other batch formulation. Batch F3 showed 101.2 ±1.05%. drug release in 60 min. The results indicated that as the concentration of superdisintegrant increased the drug release was also increased. The results of in vitro drug release of tablets was shown in figure 2.

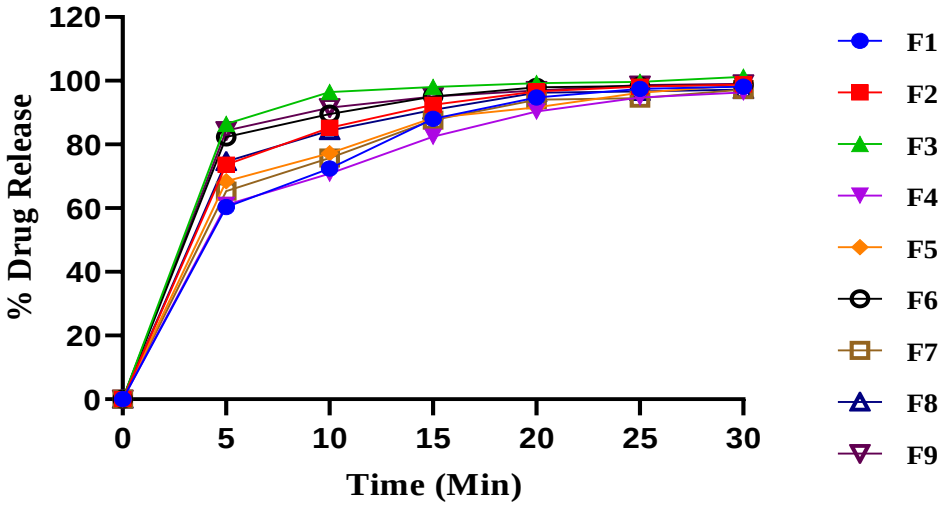

Fig.2- Comparative In vitro Dissolution Profile of formulation F1to F9

Comparative Study of Optimized Formulation with Standard Marketed Formulation

Comparative study between the optimized cefixime orodispersible kids tablets formulation (F3) and standard marketed cefixime dispersible kids tablets formulation (Hifen 100 DT, Hetero Drugs, Ltd), the comparative in vitro dissolution study was determined between two formulations. 6.8 pH buffer solution was chosen as medium of study. The optimized formulation (F3) showed 101.2 ±1.05 % drug release in 60 min. Marketed formulation (Hifen 100 DT) gives the drug release of 99.25 ± 2.89 % in 60 min. Both formulation showed almost identical pattern of drug release, which confirmed the effective development of cefixime orodispersible tablets formulation using croscarmellose sodium as superdisintegrant. Further to analyzed the dissolution parameter of two product, Similarity factor (f2) was calculated. Results showed that f2 value was found to 74 which indicate significant similarity between two formulations. In-vitro comparative dissolution study suggests, similarity between optimized formulation (F3) and marketed product (Hifen). The data of dissolution study of both formulation was given in figure 3.

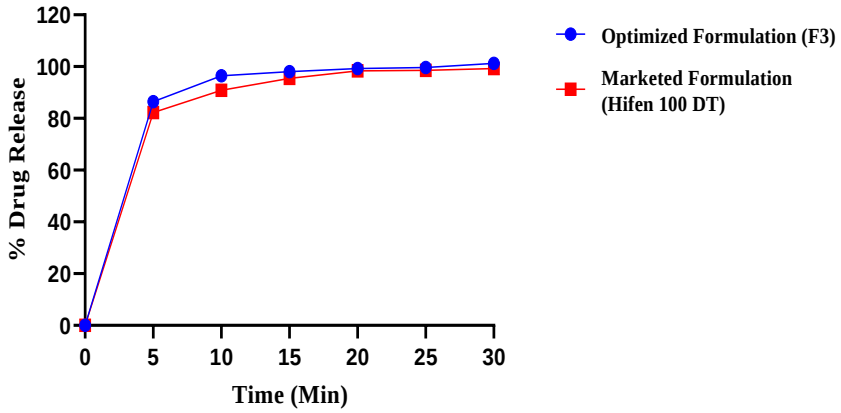

Figure 3: In vitro Comparative Dissolution Study of Optimized Formulation (F3) and its marketed formulation (Hifen 11 DT)

Further formulation F3 was subjected to stability studies for the period of three months at 40^0/75 % RH and were analyzed after specific time period of thirty days' interval. No significant changes were seen in hardness, wetting time, in vitro disintegration time and in vitro drug release after three months. Overall results indicate that formulation F3 is stable.

IV. CONCLUSION

The Cefixime orodispersible kids tablets were made using the direct compression method using superdisintegrants addition method. All batch formulations showed faster weeting time and disintegration time. Decreased in in vitro disintegration time and faster drug release was observed with increase in super-disintegrant concentration in all batches. Formulation F3 was considered as the ideal formulation which exhibited lowest disintegration time and shows 101.2 ±1.05% drug release in 30 min. Hence from this investigation it was concluded that super-disintegrants addition method using different superdisintegrants like croscarmellose sodium, sodium starch glycolate and L-HPC was found effective in the development of cefixime orodispersible kids tablets for enhance patient compliance.

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