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Formulation & Evaluation of fast dissolving tablets of Ketotefan fumerate using coprocessed superdisintegrants

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Abstract
This research involves preparation of mouth dissolving tablets of Ketotefan fumerate by direct compression method using various concentrations of co-processed superdisintegrants i.e. Sodium starch glycolate and crospovidone prepared by different methods *viz*. Microwave and Lyophilization. SSG and crospovidone used in different ratio (1:1, 1:2, 1:3, 2:1, 2:2, 2:3, 3:1, 3:2 and 3:3). The tablets were evaluated for parameters like thickness, hardness, friability, *In vitro* & *In vivo* disintegration time, wetting time, water absorption ratio, % drug content and *In vitro* drug release studies. Based on the results, formulation containing 6% superdisintegrants in combination (CP:SSG = 3:3) (KL-9) was identified as ideal and better formulation among all formulations developed for Ketotefan fumerate tablets. *In vitro* release of optimized formulation of Ketotefan fumerate Mouth dissolving tablets (KL-9) prepared by lyophilized technology was found to be 99.89% drug release within 15minutes and *in-vitro* disintegration time being ranges between 33-35sec. Though formulation KM-9 also showed good release (97.02%) prepared by microwave technology but since the release rate & disintegration profile is comparatively poor hence it is not selected. Optimized formulation KL-9 showed very good stability profile. From this observation it was concluded that the formulated tablets of Ketotefan fumerate (KL-9) were superior, economic and effective in achieving patient compliance.

Keywords: Ketotefan fumerate, fast dissolving, antihistaminic, co-processed superdisintegrants

Introduction

Drugs are rarely administered in their original pure state due to various issues like stability, proper dose strength, etc. They are administered in various dosage forms after converting it into a suitable stable formulation [1]. The aim of dosage form is to administer a drug at a therapeutic concentration to a particular site of action for a specified period of time [2]. Oral routes of drug administration are widely used up to 50-60% of total dosage forms [3].

MDT is not only indicated for people who have swallowing difficulties, but also are ideal for active people [4]. Mouth dissolving tablets are also called as fast-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 [5].

In the present investigation, the preparation and evaluation of fast dissolving tablets by using coprocessed superdisintegrants containing crospovidone and sodium starch glycolate was studied. The reasons for selection of crospovidone are high capillary activity, pronounced hydration capacity and little tendency to form gels [6]. Sodium starch glycolate was chosen because of its high swelling capacity [7]. The concept of formulating fast dissolving tablets (FDT) of metoclopramide hydrochloride (anti-emetic) [8] using co-processed superdisintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique. Various coprocessing techniques used are Solvent Evaporation, Microwave and Lyophilization.

Nausea and vomiting are the most commonly occurring symptoms in majority of pathophysiological conditions such as motion, cancer, pregnancy, and postoperative conditions. Nausea refers to feeling of impending vomiting. Vomiting refers to forceful expulsion of contents of the stomach and the proximal small intestine [9].

Antiemetic drugs are used to prevent or suppress vomiting. They act by blocking several receptors located in vomiting centres such as H1 histaminic, dopamine D2, 5-HT3 receptor, muscarinic, and neurokinin1(NK1) receptor. Drugs such as Anticholinergics, H1-antihistamines, Neuroleptics, 5-HT3 antagonists act by penetrating blood brain barrier which leads to sedation [10].

Ketotifen fumarate is an antihistamine and mast cell stabilizer used to treat allergic conditions like allergic conjunctivitis, allergic rhinitis, and asthma. It works by blocking histamine H1 receptors and preventing the release of inflammatory mediators from mast cells, which helps reduce symptoms.

Materials & Methods

Materials Ketotefan fumerate (API) was obtained as a gift sample from Torrent Pharmaceuticals (Ahmedabad, India) and other excipients Sodium Starch Glycolate, Crospovidone, Mannitol, Microcrystalline Cellulose, Talc, Magnesium Stearate, and Lactose were procured from R.S. Enterprises, Jaipur, India manufactured by Central Drug House (P) Ltd – CDH, New Delhi, India. All chemicals used were of analytical grade.

Methods

Preparation of physical mixture and co-processed superdisintegrants The physical mixture of sodium starch glycolate and crospovidone was prepared by mixing them together in glass pestle motor. The coprocessed superdisintegrant was prepared by Microwave &

Lyophilized Technology. Blends of SSG and crospovidone in different ratio (1:1, 1:2, 1:3, 2:1, 2:2, 2:3, 3:1, 3:2 and 3:3) were prepared.

Preparation of fast dissolving tablets The tablets were prepared by using single punch tablet machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 200 mg each with a diameter of 5 mm. A minimum of 50 tablets were prepared for each batch. Before compression tablet blends were evaluated for mass-volume relationship (Bulk density, Tapped density, Hausner's ratio, Compressibility index) and flow properties (Angle of repose).

The superdisintegrants (Sodium Starch Glycolate and Crospovidone) coprocessed by various techniques were used to develop the tablets. All the ingredients were shown in Table 1 were passed through sieve no. 60 and were co-grounded in a glass pestle motor [13, 15].

Table 1: Composition of MDT with Coprocessed* Superdisintegrants

Ingredients	KM1 KL1	KM2 KL2	KM3 KL3	KM4 KL4	KM5 KL5	KM6 KL6	KM7 KL7	KM8 KL8	KM9 KL9
Drug	1	1	1	1	1	1	1	1	1
SSG	1	1	1	2	2	2	3	3	3
Crospovidone	1	2	3	1	2	3	1	2	3
Avicel PH 102	25	25	25	25	25	25	25	25	25
Mannitol	30	30	30	30	30	30	30	30	30
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg. stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lactose (qs)	100	100	100	100	100	100	100	100	100
Ratio(SSG:CP)	1:1	1:2	1:3	2:1	2:2	2:3	3:1	3:2	3:3
% superdisintegrant	2	3	4	3	4	5	4	5	6

*M indicates microwave technique, L indicates lyophilized technique

Nine MDT formulations each weighing 100 mg, were prepared by using constant amount(50mg) of Ketotefan fumerate, along with a mixture of Crospovidone, Sodium starch Glycolate at different concentrations *viz*. 2,3,4,5 & 6% as these superdisintegrants work best in between range of 2% to 8%. Powdered blends, each weighing 100 mg, were then directly compressed using a single punch tablet machine equipped with convex shaped punches with a die diameter of 10 mm. Machine settings were adjusted to get the desired hardness value, which gives an intact tablet.

Evaluation Parameters

1. **Evaluation of Powder Blends:** All formulation powder bland batches were evaluated for precompression studies *viz*. angle of repose, bulk density, tapped density, Carr's consolidation index, and Hausner's ratio as per the official methods.

Flow property of all formulation batches for preparing tablets by direct compression technique was accessed through the parameters like Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's ratio. Results were shown in table 2 & 3.

Table 2: Pre-compression characterization of different batches blend of Ketotefan fumerate MDT (Microwave Technology)

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
KM1	0.451	0.489	25.49	1.08	8.79
KM2	0.462	0.506	23.21	1.10	9.11
KM3	0.464	0.518	24.16	1.12	11.05
KM4	0.467	0.507	25.57	1.09	8.7
KM5	0.485	0.532	23.41	1.10	9.36
KM6	0.469	0.513	26.95	1.09	9.3
KM7	0.467	0.512	25.57	1.10	9.52
KM8	0.477	0.514	26.09	1.08	7.95
KM9	0.473	0.518	24.16	1.10	9.36

Table 3: Pre-compression characterization of different batches blend of Ketotefan fumerate for preparing tablets by direct compression technique (Lyophilized Technology)

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
KL1	0.448	0.496	25.5	1.11	9.68
KL2	0.459	0.513	23.22	1.12	10.53
KL3	0.461	0.525	24.17	1.14	12.19
KL4	0.464	0.514	25.58	1.11	9.73
KL5	0.482	0.539	23.42	1.12	10.58
KL6	0.466	0.52	26.96	1.12	10.38
KL7	0.464	0.519	25.58	1.12	10.60
KL8	0.474	0.521	26.1	1.10	9.02
KL9	0.47	0.525	24.17	1.12	10.48

Table 2 & 3 reported results of flow properties of powder blends for preparing tablets by direct compression technique. It was found that all the batches exhibited acceptable flow property with respect to angle of repose, Carr's index, Hausner's ratio.

2. Evaluation 0f Compressed Tablets

After compression of powder blends, all the prepared batches of MDT's were evaluated for organoleptic characteristics like color, odor, taste and physical characteristics like diameter, thickness, hardness, friability,

weight variation, disintegration time, and dissolution studies.

3. Shape and Colour of Tablets

Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for colour. Tablets showed flat, circular shape & in white colour.

4. Thickness Test

Average tablet thickness (Table No. 4 & 5) was found to be consistent throughout the batch. Tablet thickness ranges between 2.07mm to 2.16mm.

5. Hardness Test

The results of hardness are given in Table No. 4 & 5. Hardness test was performed by Monsanto tester. Hardness was maintained to be within 2.00 kg/cm^2 to 4.20 kg/cm^2, as these tablets are rapidly disintegrating. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness.

6. Friability Test

The study results are tabulated in Table No. 4 & 5, was found well within the approved range (<1%) in all the formulation [16].

7. Weight Variation Test: 83

20 tablets from each formulation were randomly selected to calculate average weight and standard deviation. All the formulations exhibited uniform weight (as per IP-2010) with low standard deviation values (Table No. 4 & 5). It was found between 200mg to 204mg, indicating the uniformity of the tablets prepared by direct compression method [17].

8. Drug Content Uniformity: 88

The drug content of randomly selected tablets was determined. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The percent drug content of the tablets was found between 96.69% - 99.79% of Ketotefan fumerate. Drug content of all the formulations was found to be within the limits (Table 4 & 5) specified in IP 2010, indicating the uniformity of the tablets prepared by direct compression method & melt granulation method [18].

9. Wetting Time: 85, 86

Wetting is closely related to inner structure of tablets. The record of the wetting time was shown in Table No. 4 & 5. The wetting time in all the formulation was very fast. This may be due to ability of swelling and also capacity of absorption of water of Superdisintegrants. [19, 20]

Table 4: Weight, Thickness, Hardness, Friability & Drug Content of tablets (Microwave Technology)

Form. Code	Uniformity of Thickness (n = 3) (mm)	Diameter (n = 3) (mm)	Hardness (n = 3) (kg/cm2)	Friability %	Weight Variation (n = 20) (mg)	Drug Content Uniformity (n = 10) (%)
KM1	2.11	7.03	2.45	0.54	101	99.64
KM2	2.13	7.03	2.23	0.51	100	96.69
KM3	2.14	7.04	2.62	0.52	102	97.58
KM4	2.16	7.02	2.51	0.51	101	99.73
KM5	2.15	7.05	2.69	0.51	102	99.79
KM6	2.13	7.00	2.25	0.55	101	98.35
KM7	2.14	7.04	2.47	0.57	103	99.26
KM8	2.12	7.02	2.53	0.59	102	97.06
KM9	2.12	7.01	2.29	0.57	104	98.87

Table 5: Weight, Thickness, Hardness, Friability & Drug Content of tablets (Lyophilized Technology)

Form. Code	Uniformity of Thickness (n = 3) (mm)	Diameter (n = 3) (mm)	Hardness (n = 3) (kg/cm2)	Friability %	Weight Variation (n = 20) (mg)	Drug Content Uniformity (n = 10) (%)
KL1	2.15	7.09	2.33	0.57	101	99.17
KL2	2.09	7.12	2.11	0.54	100	97.13
KL3	2.10	7.07	2.5	0.55	102	98.02
KL4	2.12	7.11	2.39	0.54	101	99.08
KL5	2.11	7.09	2.57	0.54	102	99.23
KL6	2.14	7.05	2.13	0.58	101	98.79
KL7	2.13	7.06	2.35	0.51	103	99.7
KL8	2.10	7.11	2.41	0.52	102	97.5
KL9	2.12	7.08	2.17	0.55	104	99.91

10. Mouth Feel and *In vivo* Disintegration Time

The internal structure of tablets, which is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration.

The results are shown in Table No. 6 & 7. This was determined as per U.S.P 30 NF 25 & Japanese Pharmacopoeia [21] for all the formulations. All formulations showed disintegration time less than 50 seconds. Formulation KM9 & KL9 showed fast disintegration compared to other formulation due to high concentration of disintegrants.

The results of both parameters are shown in Table No. 6 & 7. The prepared formulations were subjected for mouth feel. The volunteers felt good taste in all the formulations. As the drug is not bitter presence of Mannitol showed good, palatable taste.

Table 6: Results of *in vitro*, *in vivo* disintegration test with Mouth Feel (Microwave Technology)

Formulation Code	*In vitro* Disintegration Time (Sec)	*In-vivo* Disintegration Time (Sec)	Mouth Feel
KM1	46-49	30-33	Good
KM2	44-48	27-30	Good

KM3	42-44	25-27	Good
KM4	45-47	27-29	Good
KM5	43-45	26-29	Good
KM6	41-44	24-28	Good
KM7	43-45	26-28	Good
KM8	40-43	24-27	Good
KM9	38-40	20-23	Good

Table 7: Results of *in vitro*, *in vivo* disintegration test with Mouth Feel (Lyophilized Technology)

Formulation Code	*In vitro* Disintegration Time (Sec)	*In-vivo* Disintegration Time (Sec)	Mouth Feel
KL1	44-47	30-33	Good
KL2	42-45	27-30	Good
KL3	40-42	25-27	Good
KL4	41-44	27-29	Good
KL5	38-40	26-29	Good
KL6	36-39	24-28	Good
KL7	37-40	26-28	Good
KL8	35-37	24-27	Good
KL9	33-35	20-23	Good

11. *In-vitro* Dissolution or Drug release studies: [22, 23]
Studies were carried out using USP-II dissolution apparatus. Drug release studies were performed in 0.1 N HCl (1, 2, 4, 6, 8, 10 & 15min). Samples of 1 ml were taken from the medium at the definite time intervals and diluted to ten times by same dissolution media. The samples were assayed by using double beam UV spectrophotometer. Table 8 & fig. 1 showed percentage release of Ketotefan fumerate in 0.1 N HCl buffer from tablets prepared by direct compression technique (Microwave Technology) and Table 9 & fig. 2 showed percentage release of Ketotefan fumerate in 0.1 N HCl buffer from tablets prepared by direct compression technique (Lyophilized Technology). It was observed that formulation KM9 show 97.02% drug release in 15 minutes and formulation KL9 show 99.89% drug release in 15 minutes.

Table 8: Percentage release of Ketotefan fumerate in 0.1 N HCl buffer from tablets prepared by direct compression technique (Microwave Technology)

Time(min)	KM1	KM2	KM3	KM4	KM5	KM6	KM7	KM8	KM9
1	21.51	24.42	28.16	25.53	29.36	32.28	30.61	33.62	36.86
2	41.41	44.14	47.68	45.34	48.42	51.64	49.85	52.6	55.07
4	55.28	58.2	62.82	59.3	63.77	66.85	64.62	67.7	70.23
6	66.3	69.81	71.98	70.43	73.49	76.39	74.67	77.39	80.58
8	75.39	77.23	80.21	78.59	81.68	84.65	82.73	85.37	88.68
10	80.46	83.37	86.94	84.63	87.4	90.92	88.16	91.37	94.47
15	82.81	85.38	88.27	86.42	89.99	92.86	90.32	93.72	97.02

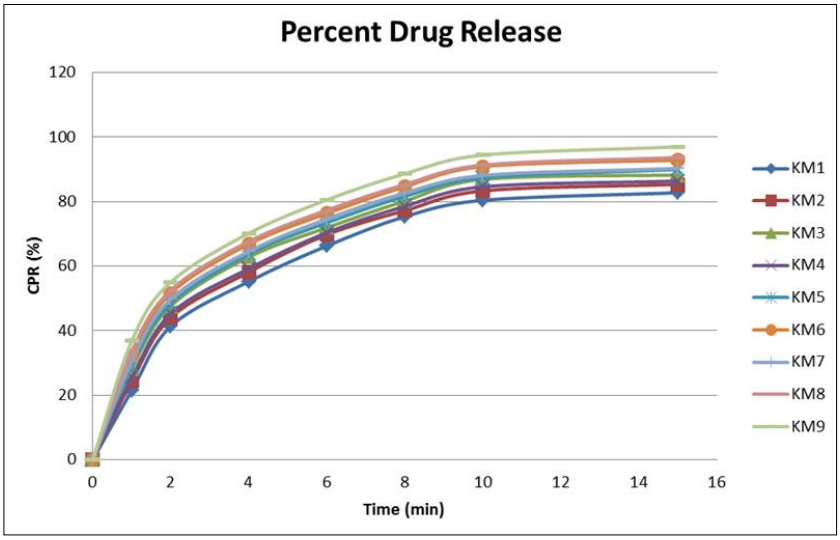

Fig 1: Percent release of Ketotefan fumerate MDTs prepared by direct compression technique (Microwave Technology)

Table 9: Percentage release of Ketotefan fumerate in 0.1 N HCl buffer from tablets prepared by direct compression technique (Lyophilized Technology)

Time(min)	KL1	KL2	KL3	KL4	KL5	KL6	KL7	KL8	KL9
1	24.66	27.57	31.31	28.68	32.51	35.43	33.76	36.77	40.01
2	44.56	47.29	50.83	48.49	51.57	54.79	53	55.75	58.22

4	58.43	61.35	65.97	62.45	66.92	70	67.77	70.85	73.38
6	69.45	72.96	75.13	73.58	76.64	79.54	77.82	80.54	83.73
8	78.54	80.38	83.36	81.74	84.83	87.8	85.88	88.52	91.83
10	83.61	86.52	90.09	87.78	90.55	94.07	91.31	94.52	97.62
15	85.96	88.53	91.42	89.57	93.14	96.01	93.47	96.87	99.89

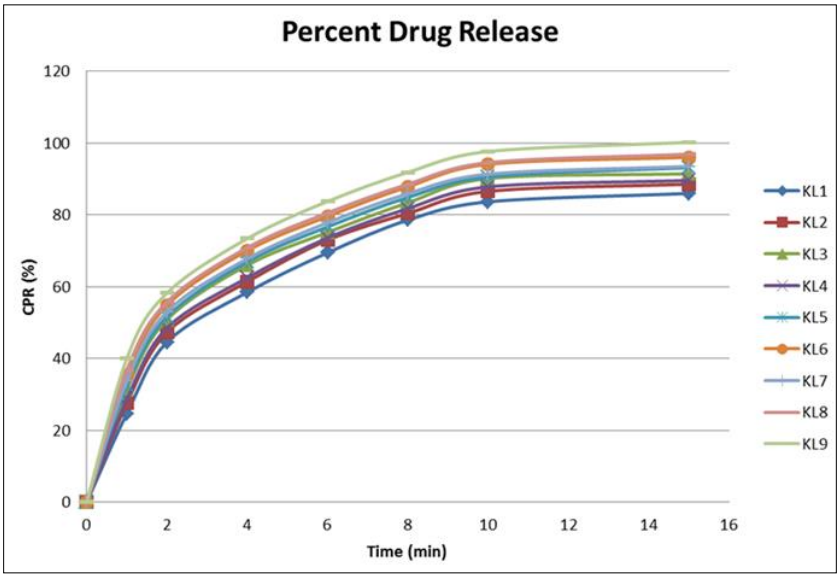

Fig 2: Percent release of Ketotefan fumerate MDTs prepared by direct compression technique (Lyophilized Technology)

Study of Release Kinetics of optimized batches 24-26

The data obtained from *in vitro* dissolution studies were fitted in different models to determine the mechanism of drug release.

Study of Release Kinetics of batch ML9

The correlation coefficient values obtained for all five models, Zero order, first order, Hixon Crowell & Higuchi models were fitted on the optimized formulations. Statistical kinetics values of batch DL9 is shown in table 10.

Table 10: *In vitro* drug release parameters for Batch ML9

Time (minutes)	Sqaure root of time	Log time	% CDR	Log %CDR	cumulative drug remaining	Log % cumulative drug remaining
0	0	0	0	-	100	2
1	1	0.00	40.01	1.602169	59.99	1.78
2	1.414214	0.30103	58.22	1.765072	41.78	1.62
4	2	0.60206	73.38	1.865578	26.62	1.43
6	2.44949	0.778151	83.73	1.922881	16.27	1.21
8	2.828427	0.90309	91.83	1.962985	8.17	0.91
10	3.162278	1	97.62	1.989539	2.38	0.38
15	3.872983	1.176091	99.89	1.999522	0.11	-0.96

Among the entire kinetic model studied for the batch (ML9), it was found that the batch followed first Order kinetics because of having maximum R^2 value of 0.9723 (closest to 1.0).

Stability Study

The stability studies carried out on optimized formulation KL9 at 40±2˚C temperature and 75±5% RH for 90 days. The formulation KL9 was showing good stability with no remarkable changes in Appearance, Drug content, Hardness and *in vitro* drug release profile.

Conclusion

Mouth dissolving tablets of Ketotefan fumerate were formulated using coprocessed super disintegrating Sodium starch glycolate & Crospovidone. Ketotefan fumerate was selected for the research work, due to less central nervous system (CNS) side-effects and better pharmacokinetic properties that are well suited for its formulation as MDT. Eighteen batches of Mouth dissolving tablets of Ketotefan fumerate were successfully prepared using sodium starch glycolate and crospovidone by direct compression method (KM1 – KM9 by microwave technology & KL1 – KL9 by lyophilized technology).

The tablets were evaluated for parameters like thickness, hardness, friability, *In vitro* & *In vivo* disintegration time, wetting time, water absorption ratio, % drug content and *In vitro* drug release studies. Based on the results, formulation containing 6% superdisintegrants in combination (CP:SSG = 3:3) (KL-9) was identified as ideal and better formulation among all formulations developed for Ketotefan fumerate tablets.

In vitro release of optimized formulation of Ketotefan fumerate Mouth dissolving tablets of DL-9 was found to be 99.89% drug release within 15minutes and *in-vitro* disintegration time being ranges between 33 and 35sec. Though formulation KM-9 also showed good release (97.02%) prepared by microwave technology but since the release rate & disintegration profile is comparatively poor hence it is not selected.

Optimized formulation KL-9 showed very good stability profile. From this observation it was concluded that the formulated tablets of Ketotefan fumerate (KL-9) were superior, economic and effective in achieving patient compliance.

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