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FORMULATING AND EVALUATING FAST DISSOLVING MOUTH DRUGS

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Abstract:

Background: *Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly.*

Objectives: *To formulate and Evaluate Fast Dissolving Mouth Drugs*

Methods: *Mouth fast dissolving tablets (MFDT's) were prepared by direct compression method according to formula. All the ingredients were passed through mesh # 30 except magnesium stearate. Magnesium stearate was passed through mesh # 40. Drug, and superdisintegrant were mixed by taking small portion of each in ascending order and blended to get a uniform mixture in a mortar. The other ingredients were weighed and mixed in geometrical order and tablets were compressed using 7mm round flat punches on a Cadmach single punch machine.*

Results: *Disintegrating study showed that the disintegrating times of the tables decreased with combination of both sodium starch glycolate and cross carmellose with different concentrations. it also showed least disintegration time in comparison with the all-other formulation because of their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates swelling action in bringing about fast disintegration*

Conclusion: *Combination of sodium starch glycolate and crosscarmellosesodium (6% of 25%-ssg&75%ccs)) promotes dissolution rate of drug release when compared to formulation of SSG &CCS alone .It may be due to capillary and wicking mechanism of SSG &CCS*

Keywords: *Glycolate, Drug delivery systems, orally disintegrating tablets, crosscarmellosesodium*

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INTRODUCTION:

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Orally disintegrating tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Orally disintegrating tablets are also known as "Mouth dissolving tablets", "Orodispersible tablets", "Melt- in-mouth Fast dissolving drug delivery, Rapimelts tablets, Porous tablets, Quick dissolving tablets" [2] etc.

Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia, and Centre for Drug Evaluation and Research (CDER). US FDA defined ODT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue". [3] European pharmacopoeia also adopted the term Orally disintegrating tablet as a tablet that is to be placed in the mouth where it disperses, rapidly before swallowing despite various terminologies used. [4] Recently, ODT have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance especially in elderly and children.[5] In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous or soft moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging. [6]

Along with the rapid market growth of ODT products, the technologies, too, have advanced considerably over the years. [7] The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs. Companies such as Eurand can produce pleasant tasting tablets, overcoming the common problem of poor drug taste compromising the benefits of an ODT. [8] In addition, some companies is developing controlled release ODTs, significantly broadening the applications of this dosage form. [9] A key reason that companies choose an ODT over other delivery technologies is that it is a relatively easy and often less risky delivery option to develop. Since the route of administration remains the same, ODTs that are formulated as bioequivalent line extensions or generic versions of an existing oral dosage form have minimal clinical requirements to gain approval. [10]

MATERIALS AND METHODS:

Materials

A. Procurement of Drug and Excipients:

The following materials and instruments used in the experiment are of laboratory grade.

Table 1: Details of materials used

Sl. No.	Materials	Source
1	Cetrizine hydrochloride	Aurobindo Pharma
2	Sodium starch glycolate	Nihal traders Hyderabad
3	Croscarmellous sodium	Nihal traders Hyderabad
4	Magnesium sterate	Span Pharma Private Limited Hyderabad, India.
5	Colloidal silicon di-oxide	Span Pharma Private Limited Hyderabad, India .
6	Lactose monohydrate	Span Pharma Private Limited Hyderabad, India .

B. Instruments and Equipment's Used:

Table 2: Details of equipments used

Sl. No.	Instruments	Manufacturer/supplier
1	UV Visible spectrophotometer	Shimadzu 1800
2	Multi station rotary punch tablet compression machine	Clit pilot press chamnnda
3	Dissolution test apparatus	Electro lab,USPTDT 06P
4	Friability Tester	Electro lab,USP EF
5	Hardness Tester	Monsanto hardness tester
6	Tablet disintegration tester	Electro lab
7	Vernier calliper	Pico.india Ltd

Method: standard punches.

Table 3: Formula of Cetirizine hydrochloride orally disintegrating tablets prepared by direct compression method

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 10	F 11	F 12	F 13	F 14	F 15
Cetrizinehydrochloride	10	1 0	10	10	10	10	10	10	10	10	10	10	10	10	10
Lactose monohydrate	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Disintegrant	2%SSG	4% SSG	6% SSG	2% CCS	4% CCS	6% CCS	2% COMBI	2% COMBI	2% COMBI	4% COMBI	4% COMBI	4% COMBI	6% COMBI	6% COMBI	6%COMBI
Colloidal silicondioxide	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052
Magnesium sterate	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052	0.052

F1= 2% of sodium starch glycolate(0.052)
F2= 4% of sodium starch glycolate(0.104)
F3= 6% of sodium starch glycolate (0.156)
F4= 2% of croscarmellous sodium(0.052)
F5= 4% of Croscarmellous sodium (0.104)
F6= 6% of Croscarmellous sodium (0.156)
F7= 2% (25:75 ratio of Croscarmellous & sodium starch glycolate) (0.125+0.039)
F8= 2% (50:50 ratio of Croscarmellous &sodium starch glycolate**)** (0.52+0.52)
F9= 2% (75:25 ratio of Croscarmellous &sodium starch glycolate**)** (0.117+0.026)
F10= 4% (25:75 ratio of Croscarmellous &sodium starch glycolate) (0.00315+0.075)
F11= 4 %(50:50 ratio of Croscarmellous &sodium starch glycolate**)** (0.052+0.052)
F12= 4% (75:25 ratio of Croscarmellous &sodium starch glycolate**)** (0.078+0.00315)
F13= 6 %(25:75 ratio of Croscarmellous &sodium starch glycolate) (0.039+0.117)
F14= 6%(50:50 ratio of Croscarmellous &sodium starch glycolate**)** (0.678+0.078)
F15=6% (75:25 ratio of Croscarmellous &sodium starch glycolate**)** (0.117+0.039)

PREPARATION OF PHOSPHATE BUFFER pH 6.8:

Dissolved 27.22 g of monobasic potassium phosphate in water and diluted to 1000 ml with water.
In 50 ml of above solution added 22.4 ml of 0.2 M sodium hydroxide solution and added water to make up 200 ml.

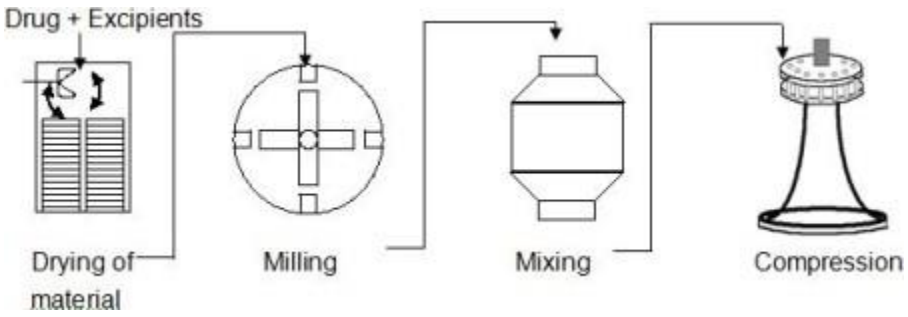
Procedure:

Mouth fast dissolving tablets (MFDT's) were prepared by direct compression method according to formula given in Table 1. All the ingredients were passed through mesh # 30 exceptmagnesium stearate. Magnesium stearate was passed through mesh # 40. Drug,and superdisintegrant were mixed by taking small portion of each in ascending order and blended to get a uniform mixture in a mortar. The other ingredients were weighed and mixed in geometrical order and tablets were compressed using 7mm round flat punches on a Cadmach single punch machine.

TABLET PUNCHING BY DIRECT COMPRESSION METHOD:

Manufacturing steps for direct compression
Direct compression involves comparatively few steps:

1. Milling of drug and excipients.
2. Mixing of drug and excipients.
3. Tablet compression.



The Orally disintegrating tablets of batch 50 of formulations of A- series and F- series were prepared by direct compression process and the composition are shown in tables --. All the materials i.e., drug, Lactose monohydrate, colloidal silicon dioxide, superdisintegrating agents were sifted through mesh no.40 and were collected in mortar and mixed well to get a uniform mixture. Magnesium stearate was sifted through mesh no.60 sieve, collected into the mortar containing other ingredients and mixed. (added lastly as it is hydrophobic may affect dissolution and disintegration profile due to more time of mixing). The lubricated directly compressible blend was compressed by using direct compression machine to get hardness above 2.5 kg/ cm^2.The tablets were sublimed at 40-50 ^{0}C in a vacuum oven for 24 hours to sublime subliming agent. End point of process is indicated by complete removal of subliming agent by sublimation.

Evaluation of Tablets:

I. Pre-compression Parameters:

Angel of Repose(θ):

Angle of repose (a) was determined using funnel method.The blend was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the heap (*r*) was measured and angle of repose was calculated.

Tan θ =h/r

Where θ is the angle of repose

Table 4: Relationship between Angle of Repose (θ) and flow properties.

Angel of Response (θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Method:

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on the graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5cm at 2 seconds intervals (Bi et al, 1995.). The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula.

LBD= weight of the powder/ volume of the packing

TBD= weight of the powder/tapped volume of the packing

Carr's compressibility Index:

Compressibility index of the powder was determined by Carr's compressibility index.

Carr's index (%) = [(TBD-LBD) X 100] / TBD

Table 5: Grading of the powders for their flow properties according to Carr's Index

compressibility Index(carr's %)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Post-compression Parameters:

Uniformity Of Weight: The test was carried out according to the Indian pharmacopoeia. Twenty tablets, from each formulation were individually weighed and the mean of tablet weight was calculated. The percentage weight variation was calculated individually comparing to mean tablet weight.

Hardness: The fracture strength, which is defined as the force required to break a tablet by radial compression, was measured with a tablet hardness tester (Monsanto hardness tester) (n=3).

Monsanto hardness tester

Phyzer type hardness tester

Friability:

The pharmacopoeial limit of friability test for a tablet is not more than 1% using Tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations).

This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

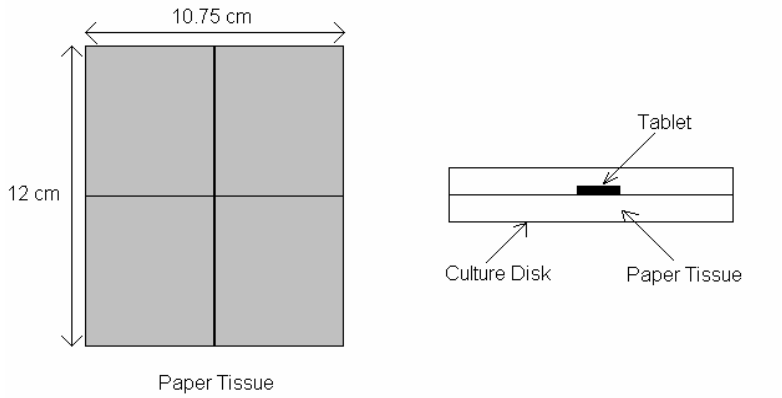
Percentage friability = 100(initial weight-final weight)/initial weight

(Or)

% Friability = (Loss in weight / Initial weight) × 100

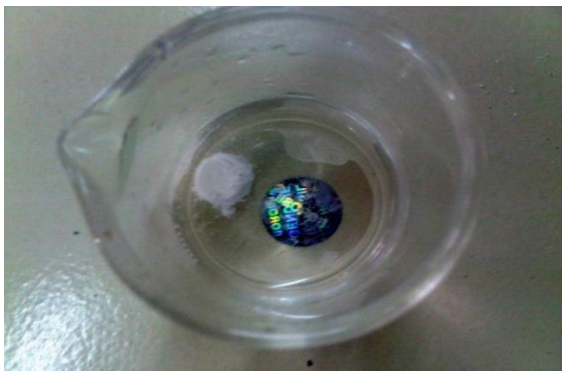
Wetting time:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper and the time required for complete wetting was measured (n=3).



Water absorption ratio:
The water absorption ratios of the tablet were carried out in petri dishes with pH 6.8 phosphate buffer. Periodically, the tablets were withdrawn from the petri dishes and weighed on electronic balance after removal of surface water by light blotting with a lab tissue for change of their weight till a constant weight is attained.

In vitro dispersion time:
In vitro dispersion time was measured by using 10ml of phosphate buffer pH 6.8 in 25 ml beaker at 37± 0.5 ˚C temperature. Time required for dispersion of the tablets was noted. In each formulation three tablets were tested (n=3).



In vitro dissolution study:
ODTs were evaluated for dissolution behaviour. Dissolution test was carried out using USP apparatus 2, paddle type. Dissolution was carried out with the rotation speed of 50 rpm using 900 ml of phosphate buffer pH 6.8 as the dissolution medium maintained at a temperature of 37 ± 0.5°C. Samples were withdrawn at predetermined time interval, diluted suitably and analyzed at 231nm for cumulative drug release using UV-Visible spectrophotometer.

RESULTS AND DISCUSSION:

Results of pre-compression parameters for Cetrizine hydrochloride tablet

Pre-compression parameters: Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters to study the flow properties of granules, to achieve uniformity of tablet weight.The results of all the preformulations parameters are given table.

Angle of repose (θ): The data obtained from angel of repose for all the formulations were found to be in the reange of 24.19° and 28.56° which reveals good flow property. All formulations showing angle of repose within 30°, indicates a good flow property of the granules.

Bulk density: Bulk density (BD) and tapped density (TD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.508 gm/cc to 0.5438 gm/cc and 0.5941 to 0.6408 respectively.

Carr's compressibility index: The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 14.30% to 17.53% had shown excellent compressibility index values up to 15% result in good to excellent flow properties. As shown in previous research work.

Results of post-compression parameters:

Hardness: The hardness of all the tablets was maintained within the 2.00 kg/cm to 4.00 kg/cm. The mean hardness test results are tabulated in table.

Friability test: The friability was found in all designed formulations in the range 0.42 to 0.74% to be well within the approved range(<1%). The friability study results were tabulated in table.

Weight variation test: The weight variation was found in all designed formulation in the range 97 to 102 mg. The mean weight variation test results are tabulated in table.

All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopeial limits.

In-vitro disintegration time: The in vitro disintegration time is measured by the time taken to undergo uniform disintegration. Rapid disintegration within several minutes was observed in all the formulations. The in vitro disintegration time of Cetrizine Hcl prepared by direct compression method by super disintegrants were found to be in the range of 18 to 11sec fulfilling the official requirements.

Based on the in vitro disintegration time , formulation F12and F15 were found to be promising and showed a disintegration time of 18 and 11 sec respectively.

Disintegrating study showed that the disintegrating times of the tables decreased with combination of both sodium starch glycolate and cross carmellose with different concentrations. it also showed least disintegration time in comparison with the all other formulation because of their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates swelling action in bringing about fast disintegration.

Wetting time: Wetting time closely related to the inner structure of the tablet. The results of wetting time are shown in table . The wetting time were found to be in the range of 11 to 18sec.

Water absorption ratio: Water absorption ratio for all the formulations found in the range 11to 16%. The results of water absorption ratio for tablets were shown in table.

Table 6: Pre-compression parameters of cetrizine Hcl tablet

Formulation code	Bulk density g/cc	Tapped density (g/cc)	Angle of repose	Carr's index(%)
F1	0.5434	0.6341	25.28	14.3037
F2	0.5212	0.6294	27.20	17.1909
F3	0.5937	0.6098	25.14	15.7592
F4	0.5098	0.5998	24.19	15.0050
F5	0.5438	0.6401	26.41	15.044
F6	0.5345	0.6296	28.56	16.296
F7	0.512	0.6210	25.71	17.5362
F8	0.5342	0.6408	26.38	16.6354
F9	0.5088	0.5941	26.01	14.3578
F10	0.532	0.581	27.01	14.343
F11	0.508	0.563	26.98	15.987
F12	0.543	0.543	26.876	14.343
F13	0.546	0.521	27.87	16.873
F14	0.576	0.587	27.97	15.876
F15	0.578	0.5876	26.87	15.871

Table 7: Post-compression parameters of cetrizine Hcl tablets

Formulation	Hardness	Frability	thickness	Weight vartiation
F1	3.5	0.69	3.21	100
F2	3.5	0.46	3.30	99
F3	4.0	0.72	3.12	101
F4	4.0	0.72	3.29	102
F5	3.6	0.68	3.34	99
F6	3..5	0.43	3.36	98
F7	4.0	0.42	3.29	99
F8	3.8	0.45	3.36	97
F9	3.7	0.54	3.30	100
F10	3.9	0.57	3.21	98
F11	3.8	0.53	3.33	100
F12	3.7	0.41	3.12	101
F13	3.5	0.52	3.42	99
F14	3.3	0.40	3.32	100
F15	3.2	0.37	3.21	102

Table 8: Post formulation studies

Formulation code	In-vitro dispersion time(sec)	Wetting time(sec)	Water absorption(%)
F1	32	27	13
F2	28	25	17
F3	26	18	18
F4	50	33	13
F5	40	25	16
F6	30	21	15
F7	30	29	14
F8	26	26	14
F9	20	20	13
F10	26	26	14
F11	24	24	13
F12	18	23	12
F13	23	20	13
F14	19	15	12
F15	11	11	11

Table 9: cumulative percentage drug release profiles

Time(sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
15	32.7	40.7	41.7	34.3	35.5	36.3	29.5	31.4	36	29	33.7	30	33.4	36.6	47.6
30	36.8	43.3	43.7	38.8	39.7	43	34.7	38.7	40.8	34	38.5	38.7	36.6	44.3	561.4
45	43.1	47.8	48.1	4.19	44.4	49.7	36	42.3	44.7	38.8	40.4	44.4	41.8	51.4	64.8
60	56.6	57.4	58.4	44	50.1	59.4	40.4	48.2	58.8	42	45	60.6	42.5	54.7	70.6
75	61	65.8	68.8	50	57	67.6	44.7	55.7	62.8	46.4	53.5	66.3	48.3	53.9	75.7
90	65.9	66.4	69.3	60.7	62.5	70.9	49	65.5	67.7	51.5	67	70.2	51.9	66.5	81
105	69.7	71	72.7	66	73	74.3	56.3	65.9	69.4	59.4	73.4	74.5	57.7	71.6	89.4
120	73.1	74.5	75.6	79	80.4	81	79.5	79.6	80.0	76	78.7	81	77	83.9	96.7

DISSOLUTION STUDY:

In vitro dissolution studies :

Dissolution rate was studied by using USP type-2 apparatus . using 900ml of phosphate buffer pH (6.8) as dissolution medium . Temperature of the dissolution medium was maintained at 37±0.5ºc, aliquot of dissolution medium withdrawn at every 15 sec interval and filtered. The absorbance of the filtered solution was measured by UV spectrophotometric method at 231nm and concentration of the drug was determined from the standard calibration curve. The dissolution of Cetirizine hydrochloride from the tablets is shown in the fig 1 cumulative percentage drug release profiles**.**

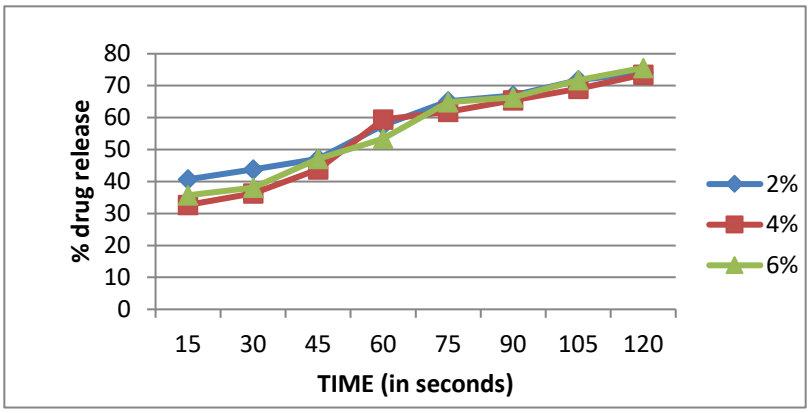


Fig 1: Release profile of formulation (F1,F2,F3)

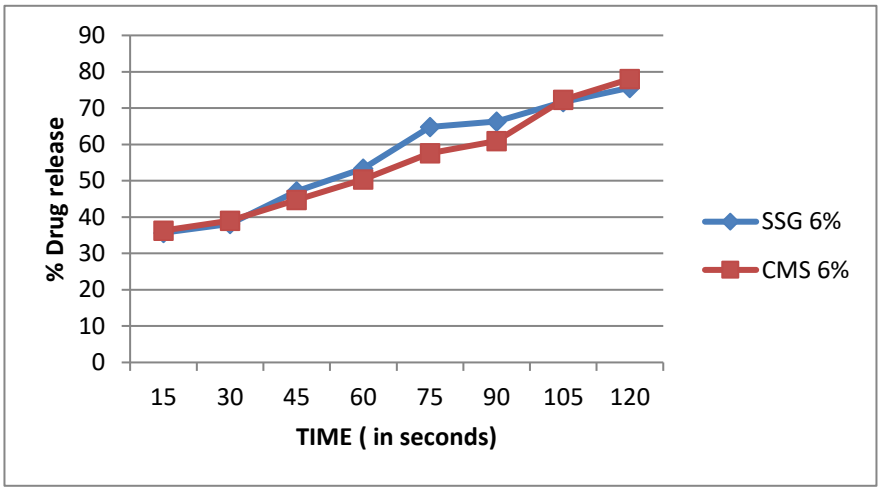


Fig 2: Release profile of formulation F4, F5, F6

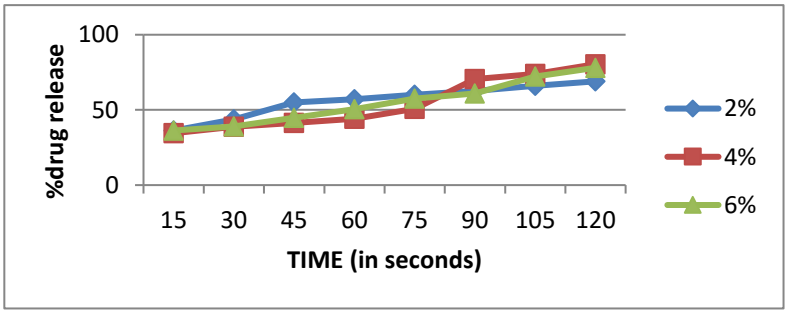


Fig 3: Release profile of formulations F1, F4

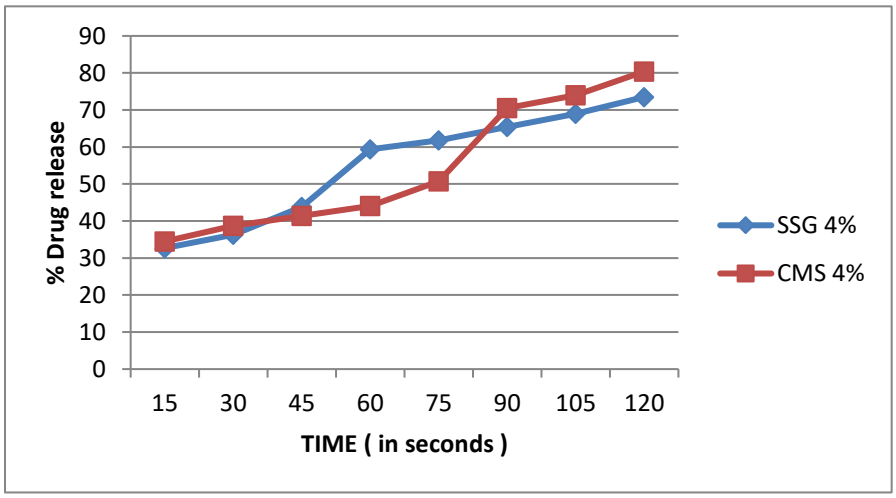


Fig 4: Release profile of formulations F2, F5

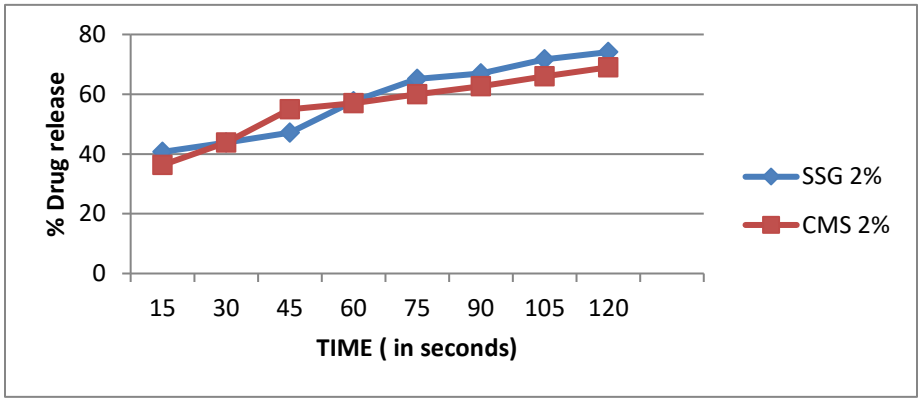


Fig 5:Release profile of formulations F3, F6

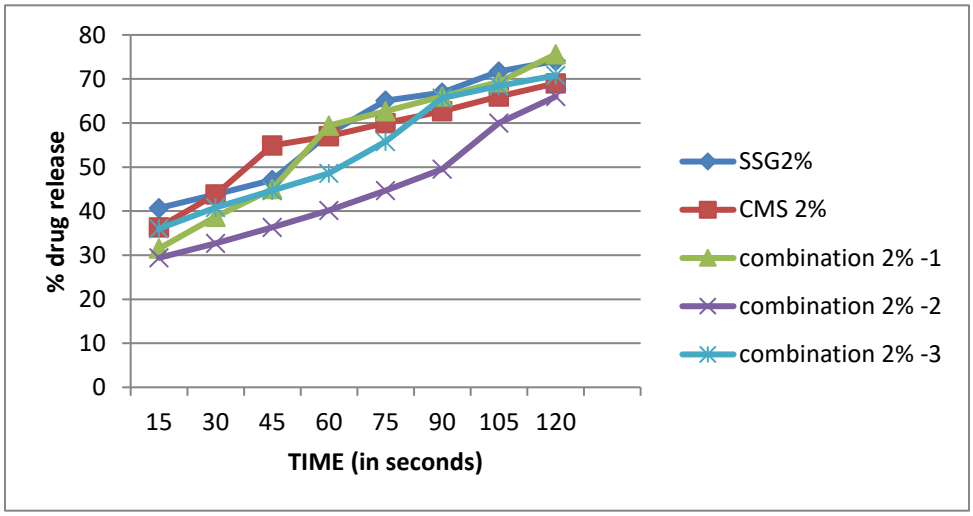


Fig 6: Release profile of formulations F1, F4, F7, F10, F13

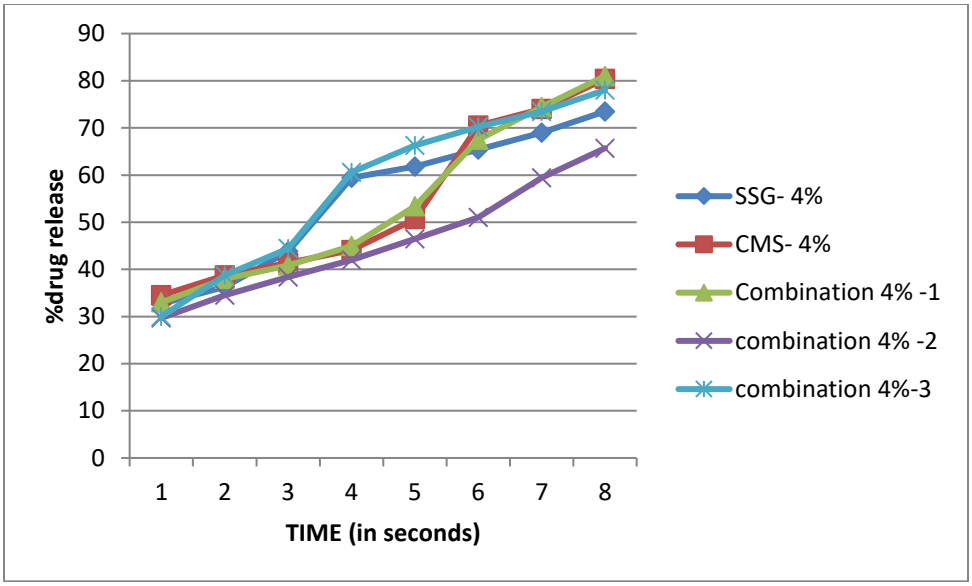


Fig 7: Release profile of formulations F2, F5, F8, F11, F14

CONCLUSION:

Fast dissolving drug system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it with water.

Combination of sodium starch glycolate and croscarmellose sodium (6% of 25%-ssg&75%ccs)) could be the alternative approach to increase the dissolution of tablets when compared to the formula with sodium starch glycolate and croscarmellose alone as disintegrant. Hence the combination of sodium starch glycolate and croscarmellose sodium (6% of 25%-ssg&75%ccs)) promotes dissolution rate of drug release when compared to formulation of SSG &CCS alone .It may be due to capillary and wicking mechanism of SSG &CCS

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