Available online on 15.12.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Comparison of Co-Processed Superdisintegrants with Superdisintegrants in Drug Release for Palatable Fast Disintegrating Oral Films of Metolazone

Nabila Quraishi*, Aimen Fatima, Shahid Mohammed

Department of Pharmaceutics, Deccan School of Pharmacy, Osmania University, Hyderabad, India

Article Info:

Article History:

Received 18 Sep 2023
Reviewed 06 Nov 2023
Accepted 24 Nov 2023
Published 15 Dec 2023

Cite this article as:

Quraishi N, Fatima A, Mohammed S, Comparison of Co-Processed Superdisintegrants with Superdisintegrants in Drug Release for Palatable Fast Disintegrating Oral Films of Metolazone, Journal of Drug Delivery and Therapeutics. 2023; 13(12):26-34

DOI: http://dx.doi.org/10.22270/jddt.v13i12.6050

*Address for Correspondence:

Nabila Quraishi, Department of Pharmaceutics, Deccan School of Pharmacy, Osmania University, Hyderabad, India

Abstract

The present study was aimed to compare co-proceesed superdisentigrant with superdisentigrants in drug release and formulate a palatable fast disintegrating oral films of metolazone and compare with standard market solid oral dosage forms. The drug was incorporated as solid dispersion to mask the bitter taste of the drug with different polymers in different ratios (PEG 4000 & Poloxomer 407) and was assessed for its taste. Metalazone with Poloxomer 407 (M-SD 5) in the ratio of 1:2 was better masked. The films were prepared by solvent casting method. HPMC E15 & Pullulan were chosen as the film forming polymers and sodium starch glycolate and crosscaramellose sodium were chosen as superdisentigrant for formulation. Pullulan (80mg) and crosscaramellose sodium (0.6%) showed the highest % drug release (99.49±0.15 within 15 min.). Therefore, this composition was chosen to prepare the film having co-processed superdisintegrants (SSG+CCS in 1:1) MF-10. MF-10 showed better disintegration (10 sec) and dissolution rate (99.12% drug release within 10 minutes.) when compared with the best formulation of superdisintigrant. All the evaluations of the optimized formulation were found to be satisfactory and within limits. MF-10 was subjected to stability studies and compared with marketed oral formulation and was found to be satisfactory.

Keywords: Metolazone, Fast disintegrating oral films (FDOFs), patient compliance, taste mask, rapidly disintegrate, co-processed superdisintegrants.

1. INTRODUCTION

There is a growing demand for novel dosage forms to cater to the needs of the paediatric and geriatric population. In order to assist or satisfy these patients, several fast-disintegrating drug delivery systems have been developed and marketed. However, such fast-disintegrating solid preparations suffer from certain major drawbacks including fear of choking/swallowing, fragility and friability and requirement of specialized and expensive packaging [1]. In order to overcome such drawbacks and satisfy the needs of the market, intraoral film has been developed. This quick disintegrating oral film can be provided in various packages convenient for use, especially for children and elders. These are thin, flexible, elegant films of various sizes and shapes, typically the size of a postage stamp meant to be placed on patient's tongue. These thin films are prepared using hydrophilic polymers, which disintegrate/disperse within few seconds when placed on the tongue without the need of water [2]. When administered to the tongue, saliva hydrates the film to disintegrate rapidly followed by natural swallowing by the subjects for absorption into the blood circulation via the gastrointestinal tract [3].

This allows minimum disintegration time in the oral mucosa in order to reach systemic circulation with the quickest onset of action. The rapid disintegrating action is mostly due to the surface area of the film wetting rapidly when exposed to the moist oral environment. FDOFs improve absorption, reduce therapeutic costs, and make administration easier, all of which patient compliance increases. Therefore, the development of FDOF containing active ingredients has received increasing attention in recent years [4].

Metolazone belongs to the drug class of thiazide-like diuretics, primarily used to treat hypertension. The dose usually starts with 2.5 mg orally once a day following oral administration it reaches to maximum plasma concentration within 2–4 hours and it has approximate elimination half-life of 14 hours. Metolazone is a bitter tasting BCS class II drug with poor bioavailability of 65% [5]. Recently solid dispersions were introduced as a taste masking technology. Where one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method [6]. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking [7]. Thus, Metolazone is taste masked here using solid dispersion technique to achieve greater patient compliance, PEG 4000 and poloxamer 407 were employed to formulate solid dispersions in drug to polymer ratios of 1:1, 1:2, and 1:3 (w/w), followed by the preparation of FDOF's.

The present study was aimed to formulate and evaluate palatable fast disintegrating oral films of metolazone and to compare the drug release of FDOF's made using co-proceesed superdisentigrant with FDOF's made using superdisentigrants.

2. MATERIALS AND METHOD

2.1. Drug and Chemicals

Metolazone was purchased from R L Fine chem, Bengaluru. PEG 4000, poloxomer was purchased from Himedia Labs Pvt Ltd. HPMC E15, pullulan, PEG 400 was purchased from MYL CHEM Mumbai. Sodium starch glycolate, crosscarmelose sodium was purchased from Hi pure fine chem. Industries, Bangalore. Vanillin & Aspartame was purchased from Universal laboritories Mumbai. All the used reagents and chemicals were of analytical reagent grade, unless otherwise stated.

2.2. Formulation of Metolazone solid dispersions

1. Metolazone solid dispersions (M-SDs) for masking bitter taste was developed by fusion method. Briefly, physical mixture of the hydrophilic carriers and drug (PEG 4000 or poloxomer 407 in ratio of 1:1, 1:2 & 1:3, drug: polymer ratio) is heated until they melt.
2. Then, this melt is cooled with continuous stirring.
3. The resultant solid mass is crushed and sieved to get solid dispersion with homogenous particle size in mesh size 80. Solid dispersion composition is shown in Table 1.

Table 1: Composition of Metolazone Solid Dispersion

Formula Code	Polymer	Drug: Polymer Ratio
M-SD 1	PEG 4000	1:1
M-SD 2		1:2
M-SD 3		1:3
M-SD 4	Poloxomer 407	1:1
M-SD 5		1:2
M-SD 6		1:3

2.3. Taste Evaluation of masked Metolazone

Taste acceptability was measured by a taste panel consisting of human volunteers(n=6) with 5 mg drug. The participants were asked to administer M-SD (5 mg) in their mouths to assess the degree of bitterness and register their scores as 0: not bitter, 1: slightly bitter, 2: bitter, 3: moderately bitter, and 4: strongly bitter and then asked to spat out and the bitterness level was recorded. The mouth was thoroughly rinsed with water, and a time of 5 min was kept between each trial.

2.4. Preparation of Co-Processed Superdisintegrants

Preparation of Croscarmellose sodium (CCS) and Sodium starch glycolate (SSG) as co-processed superdisintegrants

1. The co-processed superdisintegrants were prepared by solvent evaporation method.
2. Weighed quantity of Croscarmellose sodium + Sodium starch glycolate were mixed (in the ratio of 1:1)
3. Above mixed quantity added to the 10 ml of ethanol
4. Mixed thoroughly & stirring was continued till most the ethanol evaporated
5. The wet coherent mass was granulated through 44 mesh sieve
6. Wet granule was dried in a hot air oven at 35°C for 30 min
7. Dried granule was sifted through 80 mesh sieve and stored in airtight container for further use.

2.5. Preparation of Metolazone FDOF

Metolazone FDOF is to be prepared using solvent casting method as follows:

1. The Oral fast dissolving films were prepared by dissolving strip forming agents and plasticizer in the distilled water then solution was continuously stirred up to 4 hours on magnetic stirrer and kept for 1 hour to remove all the air bubbles entrapped.
2. Meanwhile, in the separate container remaining water-soluble excipients i.e. sweetening agent, flavor and drug were dissolved with constant stirring for 45 min.
3. When the stirring was over both the solutions were mixed together with stirring for another 1 hour on magnetic stirrer. Then the solution was kept stationary for 1 hour to let the foams settle down.
4. The resulting formulation was casted on to a plate of surface area 18 cm2. It was dried for 24 hours at room temperature.
5. The film was removed from the plate very carefully and observed for any imperfections.
6. Film was cut and stored in a butter paper covered with aluminum foil and stored in a desiccator. The composition of FDOF's is given in Table 2.

2.6. Characterization of Metolazone fast disintegrating oral films

1.Morphological studies (visual method)

Morphological studies were carried out to check color and transparency of films against a white and black background.

2. Weight variation

Weight variation was studied by individually weighing 6 randomly selected film strips using electronic weighing balance. Average weight of films calculated. The weight of each film should not deviate significantly from average weight. All measurements were done in triplicate and presented as mean ± SD.

3. Thickness test

The thickness of the polymer films was measured by using screw gauge. The thickness of each film at five different areas was determined and standard deviation was calculated. All measurements were done in triplicate and presented as mean ± SD.

4. Surface pH

pH measurement is carried out by keeping the film in contact with distilled water, and after 1 hour, the pH of the solution is measured by keeping the electrode of the pH meter in contact with the surface of the film for 60 s, and the pH of the film was noted. All measurements were done in triplicate and presented as mean ± SD.

5. Folding endurance

It is measured by repeatedly folding a film at the same point until it breaks. Folding endurance value is number of times the film is folded without breaking. This test was performed on three films of each formulation and mean ±SD was calculated. Higher folding endurance value depicts the more mechanical strength of a film [8]. All measurements were done in triplicate and presented as mean ± SD.

6. Percent elongation

On application of stress, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally,

elongation of strip increases with increasing concentrations of plasticizer [9]. All measurements were done in triplicate and presented as mean ± SD.

$$\text{Percentage of Elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100$$

7. Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile strength of the film is determined by using a tensile testing machine like the Instron or Monsanto tester. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below [10], All measurements were done in triplicate and presented as mean ± SD.

$$\text{Tensile strength} = \frac{\text{Load Failure}}{\text{Strip thickness} \times \text{Strip Width}} \times 100$$

8. In-vitro Disintegration studies

It is the time at which the film begins to break down when brought into contact with water. It can be determined by keeping a strip of the formulated Oral Film in a Petri plate containing 25 ml of distilled water at 37°C. After certain time, the film tends to disintegrate and that time was noted as disintegration time [11-12]. All measurements were done in triplicate and presented as mean ± SD.

9. Drug content

A film was taken into a 10 ml volumetric flask and dissolved in methanol (10 ml) and set aside for 2 h. Later, it was filtered through 0.45 µm membrane filter, and absorbance was checked at 260nm. All measurements were done in triplicate and presented as mean ± SD.

10. In vitro Dissolution studies

It is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media. USP – type II dissolution Apparatus is used here with Phosphate buffer pH 6.8 as dissolution medium (Volume: 900ml) & is operated at speed of 50 rpm & at a temperature of 37°C ± 0.5°C. Sample volume of 5 ml is withdrawn at 15, 30, 45, 60, 90, and 120 secs and the sink condition was maintained. The withdrawn samples were analyzed at 260 nm using ultraviolet (UV) spectrometer [13-14]. All measurements were done in triplicate and presented as mean ± SD.

11. In-vivo Taste Evaluation

Taste evaluation of all the films was done by help of human volunteers (n=10). The film was given to them for taste evaluation and result were obtained.

2.7. Comparison with Marketed Product

The Percentage Cumulative drug release of Optimized formulation was compared with that of the marketed tablets (Metez® 5mg tablets)

2.8. Stability Studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity. The stability of all the formulations will be carried out at different temperatures as per ICH guidelines. Normal room conditions at 40°C/75% RH, Long-term (25± 2°C / 60±5% RH), Intermediate (30± 2°C / 65±5% RH), Accelerated (40± 2°C / 75±5% RH) for 3 months. Formulations are packed in butter paper followed by aluminum foil [15]. After 3 months, the films are then evaluated for their appearance, surface pH, disintegration time, drug content and in vitro drug release.

Table 2 : Formulation design of metolazone fast disintegrating oral films

S.No	Ingredient (mg/film)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9	MF10
1	Metolazone (eqv.5mg)	15	15	15	15	15	15	15	15	15	15
2	SSG	1	2	4	6	-	-	-	-	-	-
3	CCS	-	-	-	-	1	2	4	6	8	
4	CCS+SSG (Co-processed)	-	-	-	-	-	-	-	-	-	6
5	HPMC E15	80	80	80	80	-	-	-	-	-	-
6	Pullulan	-	-	-	-	80	80	80	80	80	80
7	PEG-400	1	1	1	1	1	1	1	1	1	1
8	Vanillin	2	2	2	2	2	2	2	2	2	2
9	Aspartame	3	3	3	3	3	3	3	3	3	3
10	Solvent	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

3. RESULTS AND DISCUSSION

3.1. Taste Evaluation of Metolazone Solid Dispersions

M-SD 5 (Drug: PEG 4000 in the ratio of 1:2) completely taste masked the bitter taste of the drug. Therefore, this is taken for further preparations (Table 3).

Table 3: score mean values for evaluation of palatability of M-SD's (V: volunteer, scores as 0: not bitter, 1: slightly bitter, 2: bitter, 3: moderately bitter, and 4: strongly bitter)

Formula Code	Score values (by 6 volunteers)						Score mean value
	V1	V2	V3	V4	V5	V6	
Drug powder	4	4	4	4	4	4	**4.0**
M-SD 1	3	2	2	2	2	3	**2.3**
M-SD 2	0	0	1	0	0	1	**0.3**
M-SD 3	0	0	1	0	1	0	**0.3**
M-SD 4	2	2	2	2	3	2	**2.1**
M-SD 5	0	1	0	0	0	0	**0.1**
M-SD 6	0	1	0	0	0	0	**0.1**

3.2. Evaluation of the prepared Fast Disintegrating Oral Films

1. Physical appearance and surface texture

The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface, transparent and they are elegant enough to see.

2.Weight variation test

The weights of the films were found to be in the range of 102 mg±0.13 to 109±0.15. The results of average weight of all films were summarized in Table 4 and illustrated in figure 1(a). The results reveal that the average weights for all the prepared formulas were uniform and comply with referred values with very low standard deviation value, this indicates the reproducibility of the method used in the preparation of FDOF of Metolazone.

3. Thickness of films

The thicknesses of the films were in the range of to 0.16±0.12mm to 0.24±0.19mm. The results of average thickness of all films were summarized in Table 4 and illustrated in figure 1(a). A very low standard deviation value is indicating that the method used for the formulation of films is reproducible and give the films of uniform thickness and hence dosage accuracy in each film can be ensured.

4. Folding endurance

Brittle film has less value of folding endurance and good flexibility gives high value of folding endurance [16]. Folding endurance of the films was found to be > 100 (Table 4 figure 1(a)). Therefore, it can be inferred that the formulated films have good brittleness.

5. Surface pH

The pH values were found to be in the range of 6.1±0.3 to 6.5±0.1 (Table 4, figure 1(a)) making it suitable to be administered in the oral mucosa. The pH of the film nearer to the neutral region makes them comfortable for use.

6. Tensile strength

An ideal ODF should have adequate tensile strength to withstand mechanical stress, but extremely high tensile strength is undesirable because it may slow down the release of the medication from the polymer matrix. The developed ODFs had tensile strength from 1.18 ± 0.04 to 3.14 ± 0.0 N/cm2, as shown in Table 5, and illustrated in figure 1(b). It was observed that by changing the polymer types, tensile strength changed significantly. ODFs prepared with HPMC polymer had much greater tensile strength as compared with Pullulan polymer, this might be due differences in their molecular weights.

7. Percent elongation

The Percent elongation of the prepared films were found to be in the range of 18.16 ± 0.07 to 38.32 ± 0.31% (Table 4, figure 1(a)).

8. Drug content uniformity test

The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 98.2% ±0.18 to 99.9%±0.05. All the formulations were found to have drug content within limits which indicates that efficient loading and uniform distribution of drug throughout the film The results of average drug content of all films were summarized in Table 5 and illustrated in figure 1(b).

9. In-vitro disintegration test

The normal disintegration time of oral films is ~1 minute. The disintegration times of the prepared films were in the range of 14.05±1.57secs to 20.44±1.21secs. The results of average disintegration time of all films were summarized in Table 5 and illustrated in figure 1(b).

Table 4: Evaluation of Weight Variation, Thickness, folding endurance, pH, percentage elongation, (**MF1 toMF10)** (data presented as the mean ± SD, n=3)

Code	Physical Appearance	Weight of film (in mg)	Thickness (in mm)	pH	Folding endurance	% Elongation
MF1	Transparent & Smooth	102±0.13	0.19 ±0.04	6.3±0.1	102±8.14	28.19±0.21
MF2	Transparent & Smooth	103±0.27	0.20±0.08	6.3±0.2	104±10.2	24.18±0.13
MF3	Transparent & Smooth	105±0.15	0.24±0.19	6.5±0.1	107±8.24	20.11±0.51
MF4	Transparent & Smooth	107±0.16	0.16±0.12	6.5±0.1	105±12.0	18.16±0.07
MF5	Transparent & Smooth	102±0.20	0.18±0.05	6.1±0.3	105±7.22	38.32±0.31
MF6	Transparent & Smooth	103±0.17	0.19±0.17	6.2±0.2	103±10.8	36.05±0.11
MF7	Transparent & Smooth	105±0.18	0.17±0.16	6.3±0.2	102±9.16	34.19±0.21
MF8	Transparent & Smooth	107±0.17	0.20±0.12	6.4±0.1	104±6.32	30.18±0.13
MF9	Transparent & Smooth	109±0.15	0.21±0.12	6.4±0.1	102±9.26	26.11±0.51
MF10	Transparent & Smooth	**107±0.12**	**0.18±0.13**	**6.4±0.1**	**104±5.52**	**25.56±0.51**

Table 5: Evaluation of Tensile strength, Disintegration time, Drug content (data presented as the mean ± SD, n=3)

Code	Tensile strength (N/cm^2)	Disintegration (in secs)	Drug content in (%)
MF1	2.12±0.82	20.44±1.21	98.2±0.18
MF2	2.42±0.02	19.06±1.57	99.7±0.16
MF3	2.79±0.05	17.05±1.42	98.4±0.25
MF4	3.14±0.04	15.26±0.81	99.5±0.34
MF5	1.18±0.04	19.50±0.52	98.6±0.14
MF6	1.45±0.03	16.42±1.05	99.9±0.24
MF7	1.67±0.82	18.44±1.21	98.9±0.18
MF8	2.08±0.02	14.05±1.57	99.4±0.41
MF9	2.16±0.05	16.45±1.42	99.2±0.35
MF10	**2.18±0.01**	**10.23±0.51**	**99.8±0.05**

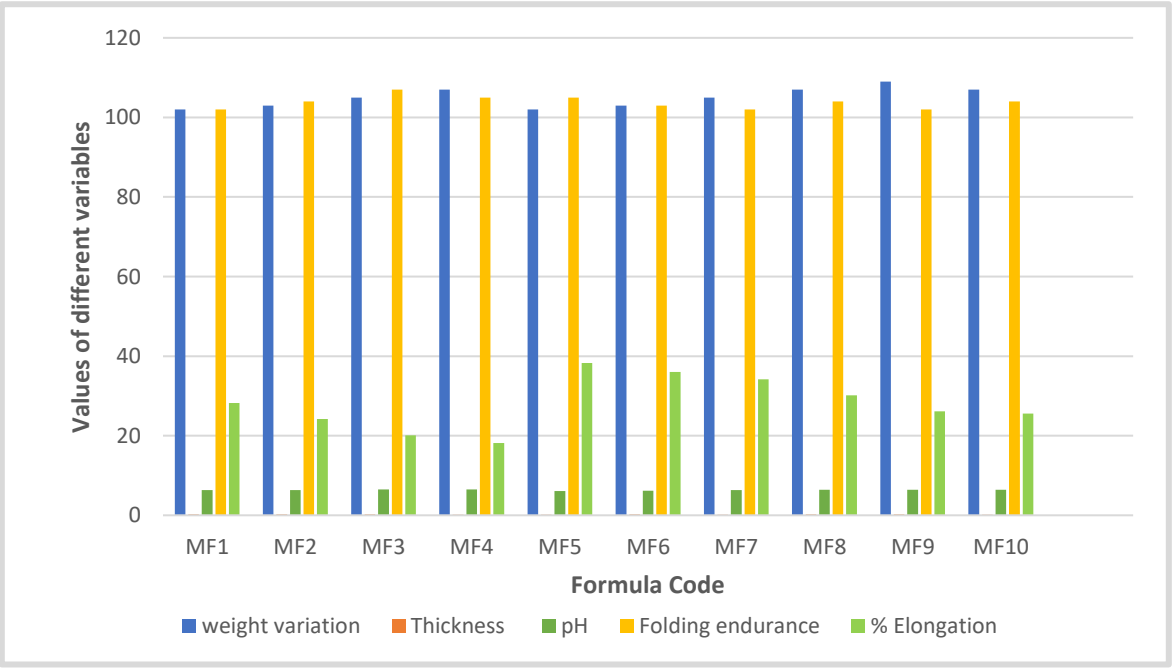

Figure 1(a): Evaluation parameters of metolazone fast disintegraing oral films

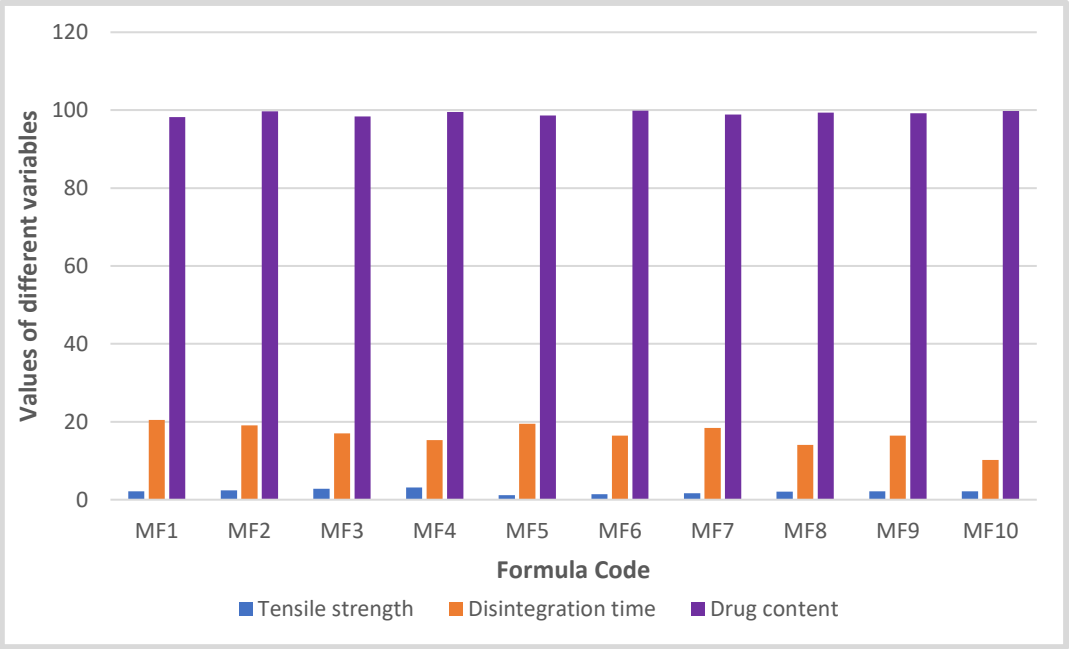

Figure 1(b): Evaluation parameters of metolazone fast disintegraing oral films

10. *In-vitro* dissolution studies

Metolazone dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm. Metolazone FDOF from each formulation was carried out in 6.8 pH phosphate buffer solution. The data of dissolution studies were summarized in Table 6. The dissolution study was conducted for 15 min. The drug release was found to be in the range of 85.26±0.17% to 100±0.11%. The plots of % cumulative drug release versus time (min) were plotted and depicted as shown in Figure 2. The formulation MF8 showed higher drug release of 99.49% revealing that films made with concentrations of Pullulan (4%w/w) and CCS (2% w/w) was the optimized formulation as it shows a higher drug release in the dissolution study. As higher dissolution rate aids in faster onset of action, MF10 was chosen as the optimize formulation.

Table 6: *In-Vitro* Dissolution Studies

Time (min)	MF1%	MF2%	MF3%	MF4%	MF5%	MF6%	MF7%	MF8%	MF9%	MF10%
2	11.28±0.07	14.25±0.06	14.24±0.11	16.32±0.15	20.31±0.06	12.61±0.15	18.74±0.14	28.94±0.07	21.19±0.05	44.19 ±0.05
4	22.17±0.12	28.26±0.14	29.26±0.31	32.18±0.18	34.12±0.13	28.47±0.18	39.81±0.12	51.27±0.09	36.21±0.12	62.21±0.12
6	39.21±0.13	39.51±0.14	42.27±0.21	43.27±0.16	47.26±0.17	48.19±0.13	57.24±0.16	72.35±0.16	55.46±0.14	75.46±0.14
8	53.38±0.15	54.28±0.15	56.69±0.21	59.62±0.13	60.12±0.14	62.28±0.17	68.28±0.18	84.26±0.18	73.27±0.16	90.27±0.16
10	60.47±0.15	65.63±0.16	68.21±0.24	69.45±0.27	75.28±0.12	80.27±0.19	85.37±0.11	92.31±0.16	84.28±0.18	99.12±0.15
15	85.26±0.17	87.48±0.16	88.49±0.17	89.25±0.12	90.33±0.14	92.49±0.11	95.35±0.12	99.49±0.15	92.12±0.20	100 ±0.11

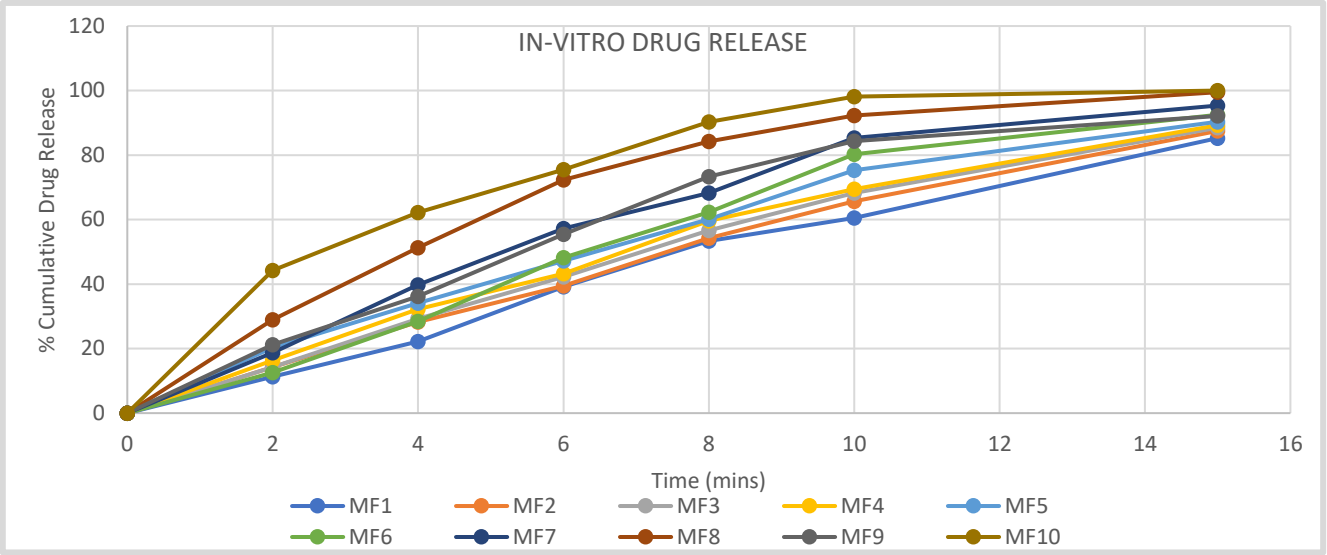

Figure 2: *In-vitro* drug release (MF1- MF10)

11. *In-Vivo* Taste Evaluation

Taste evaluation of all the films was done by help of human volunteers (n=10). A film was given to them for taste evaluation and result were obtained. The satisfactory outcomes of all the metolazone films suggested that it's taste has been effectively concealed. As given in Table 7.

Table 7: score mean values for evaluation of palatability of M-F's (V: volunteer, scores as 0: not bitter, 1: slightly bitter, 2: bitter, 3: moderately bitter, and 4: strongly bitter)

Formula Code	Score values (by 10 volunteers)										Score mean value
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
MF 1	0	1	0	0	0	0	0	0	1	0	**0.2**
MF 2	0	0	1	0	0	0	0	0	0	0	**0.1**
MF 3	1	0	0	0	0	0	0	0	0	0	**0.1**
MF 4	0	0	0	1	0	0	0	0	0	0	**0.1**
MF 5	0	0	0	0	0	0	1	0	0	0	**0.1**
MF 6	0	0	0	0	0	1	0	0	0	0	**0.1**
MF 7	0	0	0	0	0	0	0	0	1	0	**0.1**
MF 8	0	0	0	0	0	0	0	0	0	0	**0.1**
MF 9	0	0	0	0	1	0	0	0	0	0	**0.1**
MF10	0	0	0	0	0	0	0	0	0	1	**0.1**

3.3. Comparison with Marketed Product

The in-vitro dissolution study showed that there was significant increase in Metolazone drug release compared to marketed tablet (Table 8). This is illustrated in Figure 3.

Table 8: Comparison of Percentage Cumulative drug release of Optimized formulation (MF10) of Metolazone and the marketed tablet

Time (min)	% Cumulative Drug Release	
	MF10	**Marketed Tablet**
2	44.19±0.05	19.85±0.04
4	62.21±0.12	30.39±0.06
6	75.46±0.14	44.47±0.08
8	90.27±0.16	60.12±0.11
10	99.12±0.15	75.26±0.13
15	100±0.11	85.58±0.15

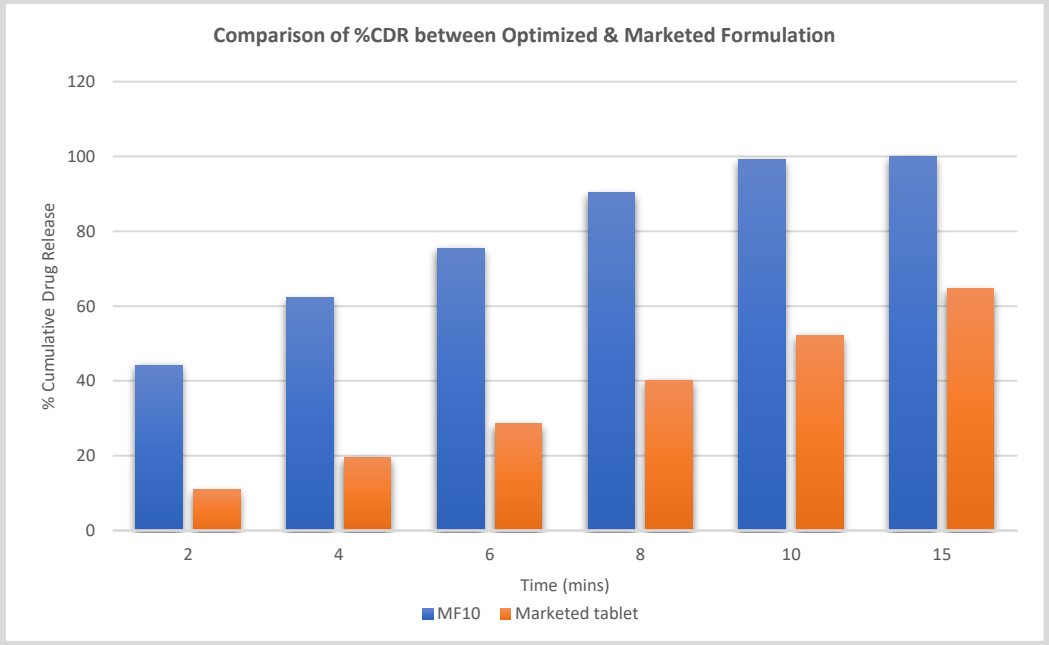

Figure 3: Comparison between %Cumulative Drug Release of optimized film and marketed tablet

3.4. Stability Studies

Stability of a drug is defined as the ability of a particular formulation, in a specific container, to maintain its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of variety of environmental conditions and enables recommended storage conditions, re-test periods and shelf lives to be established [17].

The selected optimized formulation was subjected to stability studies and the formulation was evaluated for physical appearance, surface pH, drug Content (%), disintegration Time (seconds), Cumulative Drug Release (%). (Table 9, 10, 11).

Table 9: Long-term stability studies

S.No	Tests	Initial (0 days) Room Temperature - 25±2ºC/ 60±5% RH	Storage temperature-25± 2°C / 60±5% RH		
			30th day	60th day	90th day
1	Physical Appearance	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth
2	Surface pH	6.4±0.1	6.4±0.1	6.4±0.1	6.4±0.1
3	Drug Content (%)	99.4±0.41	99.4±0.41	99.4±0.41	99.2±0.12
4	Disintegration Time (Sec)	10.23±0.51	10.23±0.51	10.23±0.51	10.28 ±0.38
5	Cumulative Drug Release (%) in 10 mins	99.12±0.15	99.12±0.15	99.12±0.15	99.09±0.09

Table 10: Intermediate stability studies

S.No	Tests	Initial (0 days) Room Temperature - 25±2ºC/ 60±5% RH	Storage temperature-30± 2°C / 65±5% RH		
			30th day	60th day	90th day
1	Physical Appearance	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth
2	Surface pH	6.4±0.1	6.4±0.2	6.3±0.3	6.3±0.3
3	Drug Content (%)	99.4±0.41	99.2±0.65	98.96±0.41	98.87±0.18
4	Disintegration Time (Sec)	10.23±0.51	10.29±0.82	10.36±0.44	10.52 ±1.63
5	Cumulative Drug Release (%) in 10mins	99.12±0.15	99.02±0.15	99.0±0.12	98.93±0.11

Table 11: Accelerated stability studies

S.No	Tests	Initial (0 days) Room Temperature - 25±2ºC/ 60±5% RH	Storage temperature-40± 2°C / 75±5% RH		
			30th day	60th day	90th day
1	Physical Appearance	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth	Transparent & Smooth
2	Surface pH	6.4±0.1	6.4±0.2	6.3±0.7	6.2±0.2
3	Drug Content (%)	99.4±0.41	98.85±0.41	98.76±0.41	98.49±0.22
4	Disintegration Time (Sec)	10.23±0.51	10.36±0.50	10.57±0.18	11.04 ±2.34
5	Cumulative Drug Release (%) in 10 mins	99.12±0.15	98.92±0.16	98.88±0.14	98.85±0.11

4. CONCLUSION

From this investigation, it can be concluded that Metolazone can be successfully formulated in to palatable fast disintegrating oral films. The bitter taste was masked effectively by using the solid dispersion method. And the film with co-processed superdisintigrant improved disintegration time and dissolution rate. Therefore, was selected as optimized formulation and was compared with the marketed tablet, revealing better drug release. Stability studies manifested that the films remained stable for duration of 3 months. Ultimately, the study supports the advancement of a pleasant-tasting and prompt onset of action Metolazone FDOF's with a promising, uncomplicated, and cost-efficient approach.

Acknowledgments

The authors are thankful to the management of Deccan School of Pharmacy, Osmania University, Hyderabad, India, for providing all the facilities to carry out this research work.

Funding source

This research did not receive any specific help like grant from funding agencies in the public, commercial, or not-for-profit-sectors.

Conflicts of Interest

The authors have no conflict of interest in relation to the publication of manuscript file.

REFERENCES

1. Desu, PK, Brahmaiah B, Nagalakshmi A, Neelima K, Nama S, Baburao C, An overview of rapid dissolving films, Asian Journal of Pharmaceutical Research, 2013; 3, 15-23. DOI: https://doi.org/10.1016/j.jsps.2015.02.024
2. Bhasin RK, Bhasin N, Ghosh PK, Advances in formulation of orally disintegrating dosage forms: a review article, Indo Global Journal of Pharmaceutical Sciences, 2011; 1(4): 328-353. DOI: https://doi.org/10.35652/igjps.2011.33
3. Gupta MS, Gowda DV, Kumar TP, Rosenholm JM, "A Comprehensive Review of Patented Technologies to Fabricate Orodispersible Films: Proof of Patent Analysis" Pharmaceutics 2022; 14(4): 820. DOI: https://doi.org/10.3390/pharmaceutics14040820
4. Harsha K, Bhairavi S, Aasavari G, Development and Evaluation of Orally Disintegrating Film of Tramadol Hydrochloride, Asian Journal of Biomedical Pharmaceutical Sciences, 2013; 3(24): 27-32.
5. Drug Bank on Metolazone; 2023. Available at: https://go.drugbank.com/drugs/DB00524.
6. Vijay DW, Shyam V. Ghadlinge, Taste Masking Methods and Techniques in Oral Pharmaceuticals: Current Perspectives, Journal of Pharmacy Research, 2009; 2(6): 1049-1054.
7. Harmik S, Yasmin S, Roop KK, Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches, Drug Development and Industrial Pharmacy, 2004; 30(5): 429-448. DOI: 10.1081/DDC-120037477 https://doi.org/10.1081/DDC-120037477
8. Farhana S, Arafat M, Saiful IP, Preparation and evaluation of fast dissolving oral thin film of caffeine, International Journal of Pharmacy Biological Sciences, 2013; 3(1): 153-161.
9. Pavani S, Goutham P, Formulation Development and Evaluation of Taste Masked Oral Disintegrating Films of Atenolol, Innovat International Journal of Medical Pharmaceutical Sciences, 2017; 2(2): 2-4. DOI: https://doi.org/10.24018/10.24018/iijmps.2018.v1i1.22
10. KM Maheswari, Pavan Kumar D, Sravanthi D, Salma S, Naga Pravallika U, Buchi NN, Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy, Journal of Pharmaceutics, 2014;1-10. DOI: http://dx.doi.org/10.1155/2014/520949.
11. Randa MZ, Munerah A, Vidya DDS, Faisal A, Majed Al, Salha MT, Musarrat HW, Alanood SA, Fabrication and characterization of orodispersible films loaded with solid dispersion to enhance Rosuvastatin calcium bioavailability, Saudi Pharmaceutical Journal, 2022; 13: 135-146. DOI: https://doi.org/10.1016/j.jsps.2022.11.012.
12. Kiramat AS, Li G, Song L, Gao B, Huang L, Luan D, Iqbal H, Cao Q, Menaa F, Lee B, Sulaiman MA, Sultan MA, Jinghao C, Rizatriptan-Loaded Oral Fast Dissolving Films: Design and Characterizations, Pharmaceutics, 2022; 14(12): 2687. DOI: https://doi.org/10.3390/pharmaceutics14122687
13. Eman Zmaily D, Affiong I, Hamad SA, Development of orally dissolving films for pediatric-centric administration of anti-epileptic drug topiramate – A design of experiments (DoE) study, Saudi Pharmaceutical Journal, 2021; 29: 635-647. https://doi.org/10.1016/j.jsps.2021.04.025
14. Muthukumar S, Hemalatha KK, Kanniyammal M, Praveena S, Vaishnavi D, Gayathri S, Kamalakkannan M, Design and Evaluation of Fast Dissolving Films Containing Itopride Hydrochloride Using Different Polymers, World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(4): 1608-1618. DOI: http://dx.doi.org/10.20959/wjpps20234-24502
15. Rajashree VL, Nikhil SL, Dr. Satish B, Kosalg, Development and Evaluation of Fast Dissolving Oral Film Containing Yohimbine Hydrochloride, International Journal of All Research Education and Scientific Methods, 2021; 9(9): 2135- 2146.
16. Muthadi Radhika Reddy, An Introduction to Fast Dissolving Oral Thin Film Drug Delivery Systems" A Review, Journal of Pharmaceutical Science & Research, 2020; 12(7): 925-940.
17. A. Deepthi, B. Venkateswara Reddy, and K. Navaneetha, Formulation and Evaluation of Fast Dissolving Oral Films of Zolmitriptan, American Journal of Advanced Drug Delivery, 2014; 153-163.