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Formulation and Evaluation of Novel Deflazacort and Tamsulosin Loaded Mouth Dissolving Films

Rajasekaran A. *, Bharathi P, Fathima Neha H, Murali S, Naresh Kumar S, Sabitha S, Thiruvengadarajan VS and.Kamaleshwari B
KMCH College of Pharmacy, Kovai Estate, Kalapatti Road, Coimbatore, Tamil Nadu, India.

***Corresponding author address**
A. Rajasekaran.
Professor, Department of Pharmaceutical Analysis
KMCH College of Pharmacy, Kovai Estate, Kalapatti Road,
Coimbatore, Tamil Nadu – 641048, India.

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KEYWORDS
Deflazacort, Tamsulosin, solvent casting, mouth dissolving films, Polyvinyl alcohol, kidney stone

ABSTRACT:

Mouth dissolving films (MDFs) is a newly emerging drug delivery system that contains a polymer to retain the dosage form which adhere to mucosa, and disintegrate quickly and releases the medication. Since Deflazacort and Tamsulosin belongs to BCS II classification, MDFs formulation was developed with the intention of obtaining better therapeutic efficiency with increase in bioavailability that can be beneficial to treat kidney stones. In this study, three MDFs with the combination of Deflazacort and Tamsulosin was formulated by solvent casting method using three different concentrations of polymer (PVA), and evaluated for various parameters such as thickness, folding endurance, surface pH, drug content, weight variation, *in vitro* disintegration and *in vitro dissolution* studies. Physical incompatibilities between API and the excipients in the films were tested using FTIR. Formulated MDFs complied with films parameters and physical incompatibilities. Among the 3 formulations, optimized formulation F2 exhibited more than 97% drug release within 10 min and disintegrated within 55 secs. Mouth dissolving films of Deflazacort and Tamsulosin were found to be suitable for eliciting better therapeutic effect for treating renal calculi.

INTRODUCTION

Mouth dissolving films is a novel drug delivery system, which readily get wetted and dissolved rapidly by saliva in mouth without intake of water. Deflazacort (DEF) is a corticosteroidal prodrug, an oxazoline derivative of prednisolone and a selective glucocorticoid receptor agonist which produces an active metabolite deflazacort-21 hydroxide *in vivo* by plasma esterase. DEF is used to manage Duchenne Muscular Dystrophy as it possesses anti-inflammatory and immunosuppressive property. Tamsulosin (TAM) is an alpha adreno receptor antagonist particularly alpha1A and alpha 1D receptors and hence used for the treatment of Nephrolithiasis. DEF and TAM tablet dosage form is used for treating Nephrolithiasis since 2017, where the mouth absorption maxima, C_{max} and t_{max} occurs after 1 hour of administration. The combination of DEF and TAM reported to possess 86% efficacy whereas TAM exhibits 52% efficacy when administered alone in patients with renal calculi. Though conventional solid mouth dosage forms are convenient, safe and most economical; slow onset of action, difficulty in swallowing and fear of choking particularly in geriatric, pediatric, bedridden, emetic and mentally retarded patients are the major issues with conventional mouth dosage forms affecting around 50% of world population[1,2]. Further, when compared to conventional mouth solid dosage forms, mouth dissolving films of DEF and TAM reaches the systemic circulation directly, thereby enhances the

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bioavailability evading its first pass effect, renders quick onset of action, fast pain relief and promotes expulsion of stones with size of ≤ 8mm. Hence, it was thought worthwhile to formulate MDFs to overcome the problems of conventional solid oral dosage forms and as a first line treatment for uretic stones with high expulsion rate with shorter the expulsion time.

MATERIALS AND METHODS:

Materials: DEF and TAM were obtained as a gift sample from Best Care Pharmaceuticals Pondicherry, India. Polyvinyl alcohol, and sodium starch glycolate (SSG) were obtained from Sigma Aldrich Chemical Co., USA. Solvents and other excipients were of an analytical grade.

Preformulation Studies

Determination of purity of APIs:

Determination of Melting point: To assess the purity of DEF and TAM melting point was determined by capillary method using digital melting point apparatus (REMI C-30BL), where the temperature at which the drugs started to melt and it completely melted was recorded[3]

Determination of λ max for Deflazacort and Tamsulosin:

DEF and TAM were dissolved separately in ethanol and diluted to get the concentration of 6 µg/ml each and λ max of the solution was determined separately by scanning them from 200 - 400 nm using methanol as blank[4]

Calibration curve

Ten mg of DEF and TAM was dissolved separately in 10 ml of methanol in a 10 ml volumetric flask and the volume was adjusted to 10 ml with methanol. Further dilutions were made using methanol to get a concentration in the range of 2 to 10 µg/ml. Absorbance of the solutions were measured at 242 nm and 214 nm respectively for DEF and TAM by UV spectrophotometer (Shimadzu 1800, Japan) using methanol as blank. The process was carried out in triplicate and calibration curve was plotted for concentration vs absorbance.

Compatibility study:

FTIR analysis: FTIR spectra (Jasco, 4600) of pure drugs and the MDFs were recorded in the transmission mode in wave number region of 4000-400 cm^{-1} to assess the interaction of the drugs, polymer and the excipients[5]

Preparation of films: MDFs was prepared by solvent casting method[6] and composition of MDFs is mentioned in Table 1. DEF and TAM were dissolved separately in ethanol. Three different formulations F1, F2 and F3 were prepared using 40%, 50% and 60% w/v PVA and the drug solution was poured into this PVA solution. Then the solution containing SSG, citric acid, methyl paraben, menthol and glycerin was added to it. Then the above solution was then poured into prelubricated Petri dish and dried to form the film at room temperature. After 24 h, the dried films were packed in aluminum pouches.

Evaluation of mouth dissolving films[7]:

Physical parameters

Morphological properties: MDFs tested for homogeneity, color, transparency, and odor.

Weight Variation.: Three films of size 2.5 × 2.5 cm^2 prepared were weighed individually on a digital analytical balance (Shimadzu, Japan) and the mean weight was computed for each batch.

Films thickness: The thickness of the mouth dissolving films was evaluated using calibrated Vernier caliper. The thickness was measured from all four corners of the film at different positions. The average readings were taken as the mean thickness.

Tensile strength: Tensile strength was measured by Universal testing machine (Instron Industrial Products, Norwood, USA). The films were fixed between the two clips, 3 cm apart, and then they were withdrawn by the upper clip at a speed of 1 mm/min until they detach. The tensile strength was calculated as an average of three measurements.

Tensile strength = Load at breakage (kg)/ Films thickness (mm) × Films width (mm) X 100

Folding endurance: This test was done to ensure that the films were flexible enough to allow for easy administration. Each film was repeatedly folded in the same manner until it breaks. The mean value (n=3) for

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three films was recorded.

Percent Moisture Loss:. The formulated films were weighed initially and placed in the desiccator containing anhydrous calcium chloride. After 3 days, the films were measured for its final weight, thus to obtain the percentage of moisture loss[8]. Three films mean weight (n=3) was calculated from the following formula and the values were recorded.

Percent Moisture content loss = initial weight - final weight /initial weight X 100

Chemical parameters[9,10]:

Surface pH. Three MDFs were taken and each strip was moistened with 4 ml of double distilled water and kept for 5 min. pH was measured by a calibrated pH meter (Eutech, India) and the mean values of three readings for each film was recorded.

Drug Content: For drug content, the films of size 2.5 × 2.5 cm^2 were cut from different positions of casted films. Each film was placed in volumetric flask containing 60 ml of 0.1N hydrochloric acid and was sonicated for 15 mins. The volume was made upto 100 ml and the absorbance of solution was measured using UV-Visible spectrophotometer at 225 nm after appropriate dilutions using 0.1N hydrochloric acid as blank. Analysis was performed three times for each film and the mean values were recorded.

***In vitro* Disintegration test:** The disintegration test was carried out by placing the mouth dissolving films of size 2.5 × 2.5 cm^2 in the glass Petri dish containing 10 ml of phosphate buffer (pH 6.8). It was stirred at every 10 secs time interval. The time required for the films to disintegrate was recorded and the results are expressed as a mean of 5 determinations.

***In vitro* dissolution study:** The *in vitro* release dissolution study was carried out using Dissolution testing apparatus. The Mouth dissolving films of 2.5 × 2.5 cm^2 size was cut and placed in dissolution medium of 900 ml phosphate buffer with pH of 6.8, agitated at 50 rpm and kept at 37 ± 0.5◦C. At predetermined time interval of 2 mins, 5 ml aliquots of samples were taken and same volume of buffer was replenished. Concentration of DEF and TAM was determined by measuring the absorbance spectrophotometrically at 225 nm. The results are expressed as a mean of 3 determinations.

Stability studies: Stability study was carried out as per ICH guidelines by storing the optimized MDFs for 3 months in the stability chamber. Physical parameters, drug content and *In vitro* drug release was determined at 0, 30, 60 and 90 days.

RESULTS

Preformulation Studies

Both DEF and TAM were found to be pure as the observed melting point of both drugs are in correlation with the reported literature.[11,12]

The λ max of DEF and TAM was found to be 242 nm and 215 nm respectively.

Linear graph plotted between concentration and absorbance obeyed Beer's Law in the concentration range of 2 to 10 µg/ml with correlation coefficient of 0.9979 for DEF and 0.9996 for TAM respectively (Figure 2 and 3).

FTIR Compatibility study:

The ATR spectra of pure DEF and TAM showed the peaks corresponding to the functional groups in the structure of the drugs. No additional peaks were observed in the ATR spectrum of MDFs confirming no incompatibility of drugs with the excipients employed in the formulation (Figure 4 - 8)

Evaluation of MDFs loaded with DEF and TAM

Physical parameters:

Morphological properties: The prepared MDFs (Figure 1) were observed to be soft, flexible, and transparent with slightly sweet taste.

Weight Variation: The weights of the mouth dissolving films were measured as 0.09 ± 0.004, 0.122 ± 0.002 and 0.143 ± 0.002 g for F1, F2 and F3, respectively.

Thickness: The thickness of the prepared mouth dissolving films was measured as 0.1 ±0.015, 0.1 ± 0.010 and 0.1 ± 0.010 mm for F1, F2 and F3 respectively.

Tensile Strength: The tensile strength of the prepared MDFs was found to be 1.156 ± 0.0501, 1.452 ±

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0.0745&1.234 ± 0.0451 respectively for F1, F2 & F 3. The tensile strength increased as the polymer concentration of mouth dissolving films increased. The obtained tensile strength may support the transport and storage of mouth dissolving films without tearing.

Folding Endurance: The folding endurance of the films indicates the brittleness of the films, and is an important indicator of mechanical strength, which could be damaged during transportation and storage. Higher value of folding endurance indicates that the formulated films were strong to withstand handling. The folding endurance of the prepared mouth dissolving films was measured as 180 ± 17, 200 ± 19 and 200 ± 13 folds for F1, F2 and F3 respectively. The folding endurance was noted to be increased as the thickness of the mouth dissolving films increased.

Percent moisture loss: The percent moisture loss was found to be 1.18 ± 0.01, 1.03 ± 0.02 & 1.11 ± 0.02 for F1- F3 respectively.

Chemical parameters:

Surface pH: The surface pH of the formulations was found to be5.8±0.02,6.3 ± 0.04 &6.39±0.01 for the formulation F1, F2 and F3 respectively.

Drug content: The percentage drug content of the MDFs was found to be 92 ± 0.5, 98 ± 0.5 and 93 ± 0.5 % for F1, F2 and F3 respectively.

***In vitro* Disintegration test:** In vitro disintegration time for the mouth films is about 49, 55 and 59 secs for F1, F2 and F3 respectively. It was observed that disintegration time of the films increased with increase in the polymer concentration. Higher the concentration of polymer prolongs the disintegration time. (Table 2)

***In vitro* Dissolution study:** The dissolution studies were performed using type I dissolution apparatus (basket) and phosphate buffer at pH 6.8 was used as a medium, and the amount of drug release were tabulated (Table 3). The percentage drug release from mouth dissolving films was 86.23, 98.38 and 90.16 % for F1, F2 and F3 respectively at the end of 10 minutes (Figure 9)

Stability studies: Stability study was carried out as per ICH guidelines by storing the optimized MDFs at 25 ± 2 ° C / 60 ± 5 % RH and 40 ± 2 ° C / 75 ± 5 % RH for 3 months in the stability chamber. Physical parameters, drug content and *In vitro* drug release was determined at 0, 30, 60 and 90 days.

DISCUSSION

Mouth Dissolving films is one of the novel dosage forms, designed to be placed in mouth where they rapidly disintegrate, release the medication quickly, and hence offer's advantages of enhanced bioavailability as they bypass the first pass metabolism, improved patient compliance and provide user-friendly alternative to traditional dosage forms like tablets and capsules.

Innovative new approaches in drug delivery, is an important concern for the large users of medicines, particularly the geriatric patients. MDFs were useful for patients who have difficulty in swallowing or require a fast-acting delivery of a drug.

Oral bioavailability of DEF is 68% and maximum plasma concentrations of active metabolite deflazacort-21-hydroxide was reported as 121 µg/L after a single 30 mg oral administration of DEF[13]. Oral administration of TAM causes change in pH as it passes from the stomach to intestine and hence affects the drug solubility and oral bioavailability. The secondary amino and sulfonamide groups present in TAM enact as proton binding sites and enhance the solubility of TAM under acidic conditions[14]. Thus, to enhance the oral bioavailability, MDFs loaded with DEF and TAM was formulated.The characterization studies confirmed the purity of API and all the excipients used in the formulation. FTIR studies also confirmed the compatibility of API with all other excipients, as it does not show any changes in the spectrum. In this study, MDFs containing DEF and TAM were formulated using polymer PVA, sodium starch glycolate, citric acid, menthol, methylparaben, glycerin and ethanol. Selection of polymer is an important criterion as various hydrophilic polymers like Polyethylene glycols, Polyvinylpyrrolidone, Polyvinyl alcohol and Hydroxypropyl methylcellulose used in the preparation of MDFs improve the solubility of drugs. PVA was used for the preparation of mouth dissolving films as it provides transparent appearance, folding endurance greater than 300, disintegration time around 60 secs, better flexibility, biocompatibility and better solubility. Three formulations coded as F1, F2 and F3 in 3 different concentrations of PVA viz. 40, 50 and 60 % respectively were developed. Glycerin at 5% of the total weight of the formulation was used as plasticizer to

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improve the tensile strength. Though the other plasticizers like PEG, diethyl phthalate, triethyl citrate, tributyl citrate can also be used for developing MDFs, glycerin was preferred as it also acts as a co-solvent and enhances dissolution of DEF and TAM causing rapid disintegration of MDFs. Sodium starch glycolate, citric acid, methyl paraben and menthol were used as plasticizer, disintegrant, saliva stimulating agent, preservative and flavoring agent respectively in the formulation of MDFs. MDFs can be prepared by solvent casting method, semi-solid casting method, hot-melt extrusion method, solid dispersion extrusion method, rolling method. Solvent casting method was adopted in this study for preparation of MDFs of DEF and TAM[6].The formulated MDFs were evaluated for various parameters like weight variation, thickness, tensile strength, folding endurance, percent moisture loss, surface pH, drug content, *in vitro* disintegration and *in vitro* dissolution. The weight of the optimized F2 film determined for 3 times was found to be constant which confirmed the film contains uniform amount of API and excipients. Uniformity of film was governed by thickness and it should not be too thick or too thin as it may not disintegrate properly or it will be difficult to remove without damage. The results of the mechanical properties viz., tensile strength and folding endurance revealed that the formulation has good film property and elasticity. Percentage moisture loss of 1.03 of the optimized film formulation F2 was found to be within the limits[15]. Surface pH of the prepared MDFs complied with the salivary pH range, and thus confirm nonirritant to oral mucosa. The drug content and *In vitro* drug release was determined at isosbestic point 225 nm. Drug content of the optimized film F2 98 ± 0.5 was found to be within the limits. *In-vitro* drug release of the optimized film F2 98.38% at the end of 10 minutes. The mean disintegration time of F1, F2 and F3 MDFs were 49 ± 3, 55 ± 4 and 59 ± 1 secs indicating that the disintegration time is directly proportional to the polymer concentration. This may be attributed due to the high degree of hydrolyzation of PVA. The results of the evaluation parameters including stability studies for MDFs were found to be within acceptable range.

CONCLUSION

MDFs loaded with DEF and TAM was formulated to facilitate expulsion of renal calculi as these combinations were employed as first-line drug for the medical expulsion therapy and as an adjuvant to facilitate stone expulsion after percutaneous and shockwave lithotripsy. The optimized formulation F2 exhibited 97% drug release within 10 min and disintegrated within 55 secs and thus found to be suitable for eliciting better therapeutic effect for treating renal calculi. The conclusion of the study revealed that, the developed mouth dissolving films (MDFs) containing DEF and TAM shown excellent uniformity in content, exhibited adequate mechanical strength and provided fast disintegration on hydration.

DISCLOSURE OF INTEREST:

The authors declare that there is no conflict of interest.

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Formulation	Deflazacort (mg)	Tamsulosin (mg)	PVA (%)	Glycerin (%) as Plasticizer	Sodium starch glycollate as disintegrant (%)	Citric acid as Saliva stimulating agent (%)	Menthol as Cooling agent (%)	Methyl paraben as Preservative (%)	Ethanol as solvent (ml)	Weight of film (mg) (n=3)
F1	30	0.4	40	5	5	2.5	0.4	0.01	qs	90 ± 0.004
F2	30	0.4	50	5	5	2.5	0.4	0.01	qs	122 ±0.002
F3	30	0.4	60	5	5	2.5	0.4	0.01	qs	143 ±0.002

Table 1. Composition of Deflazacort and Tamsulosin loaded MDFs

Table 2. Evaluation parameters of the prepared MDFs.

Formulation	Physical parameters					Chemical parameters		
	Weight Variation (g)	Thickness (mm)	Tensile strength (MPa)	Folding endurance (folds)	Percent Moisture loss	Surface pH	Content Uniformity (%)	In- vitro disintegration test (secs)
F1	0.09 ± 0.004	0.1 ±0.015	1.156 ± 0.0501	180±17	1.18 ± 0.01	5.80 ±0.02	92 ± 0.5	49±3
F2	0.122 ±0.002	0.1 ±0.010	1.452 ± 0.0745	200±19	1.03 ± 0.02	6.30 ±0.04	98 ± 0.5	55±4
F3	0.143 ±0.002	0.1 ±0.010	1.234 ± 0.0451	200±13	1.11 ± 0.02	6.39±0.01	93 ± 0.5	59±1

Data reported are mean ± standard deviation (n = 3)

Table 3. *In- vitro* drug release of MDFs loaded with DEF and TAM

Formulation	Percentage drug release (in mins)					
	0	2	4	6	8	10
F1	0	14.45	28.67	45.89	70.90	86.23
F2	0	19.30	32.42	48.54	85.42	98.38

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F3	0	18.20	30.56	47.69	82.38	90.16

Figure 1. Formulated mouth dissolving films loaded with DEF and TAM

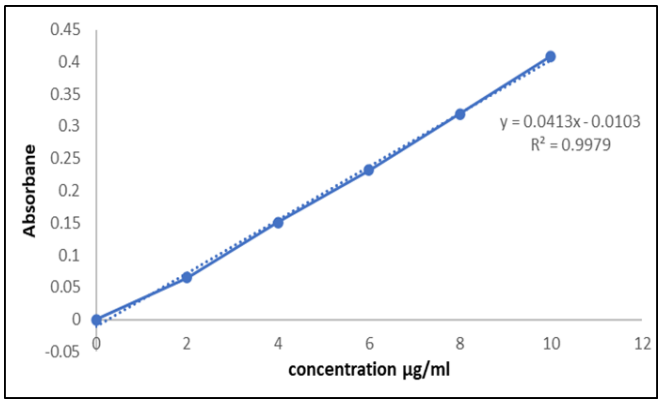

Figure 2. Calibration curve of Deflazacort

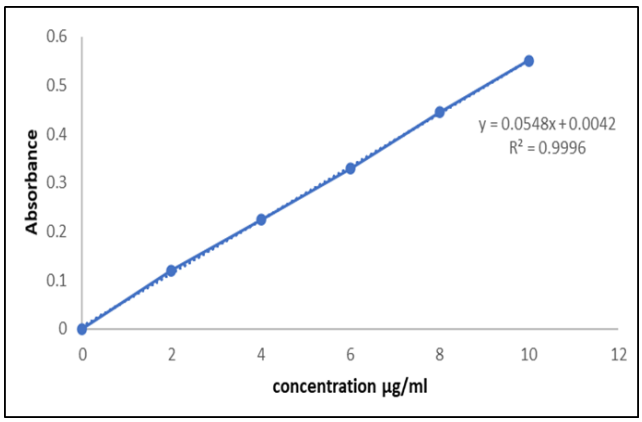

Figure 3. Calibration curve of Tamsulosin

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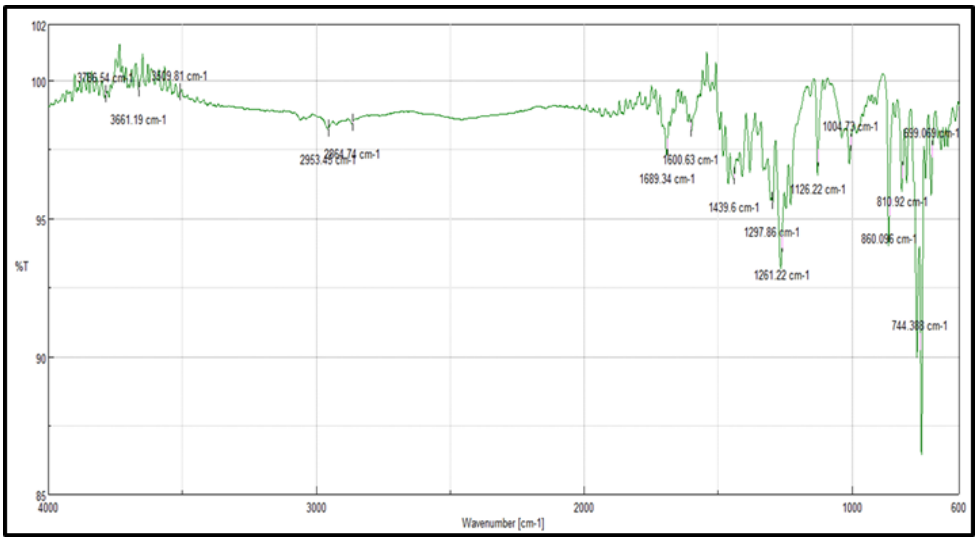

Figure 4. FTIR spectrum of Deflazacort

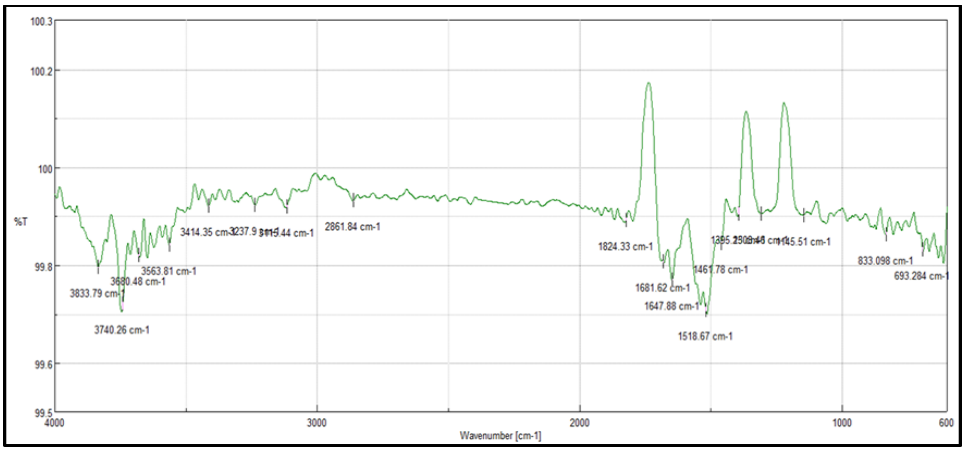

Figure 5. FTIR spectrum of Tamsulosin

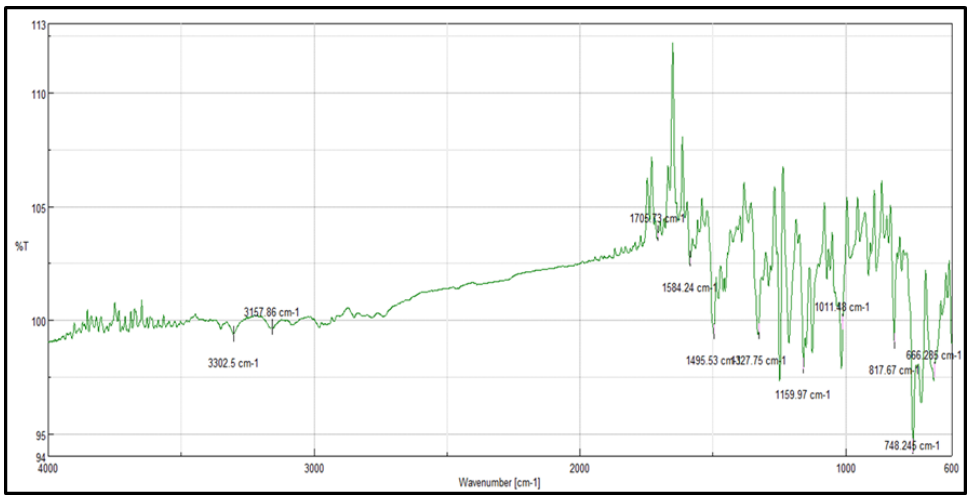

Figure 6. FTIR spectrum of Deflazacort + Tamsulosin

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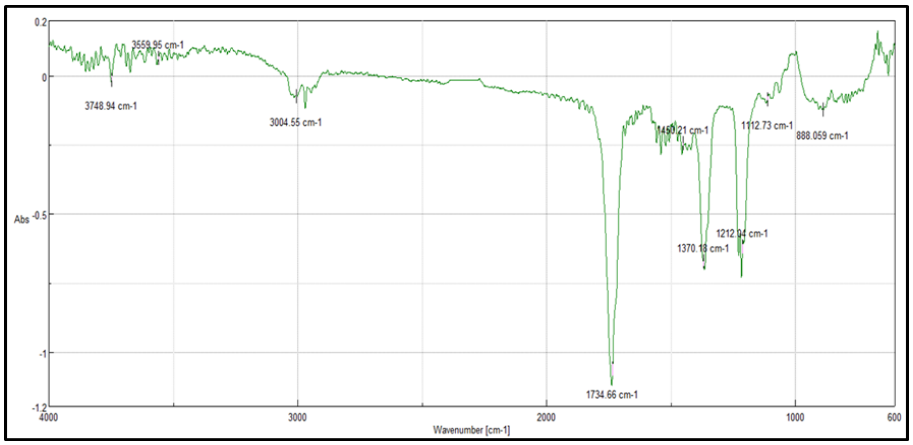

Figure 7. FTIR spectrum of PVA + SSG

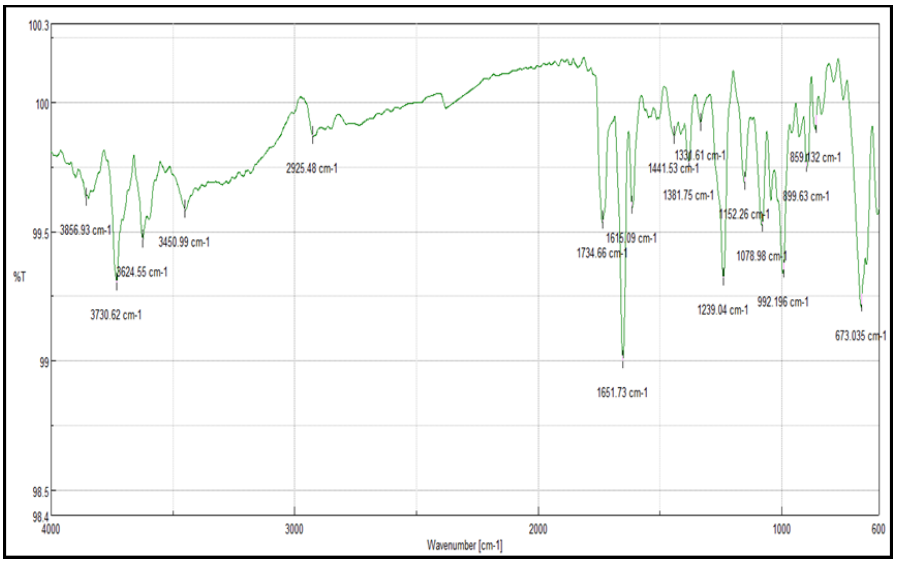

Figure 8. FTIR spectrum of Deflazacort + Tamsulosin + PVA + SSG + Citric acid

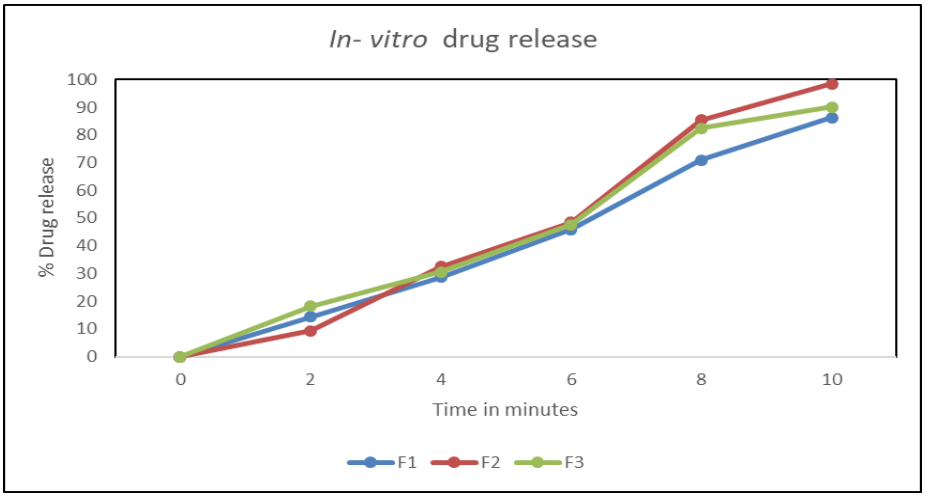

Figure 9. *In vitro* drug release profile of MDFs loaded with DEF and TAM