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DEVELOPMENT AND EVALUATION OF ORALLY DISINTEGRATING FILMS CONTAINING MOXONIDINE CHLORIDE

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ABSTRACT

The oral route is considered to be the most advantageous, inexpensive and safe method of delivery of drugs due to the highest component of compliance, especially paediatric and geriatric. The final goal of every drug delivery system is the successful delivery of the drug to the body. Orally disintegrating dosage form is the widely preferred commercial product among the various dosage forms: The oral disintegrating films (ODF) of Moxonidine Chloride (MXD)was prepared using HPMC E3, HPMC E6 and Xanthan gum. Using methanol and dichloromethane in a 1:1 ratio, the polymer solution was prepared and held aside for around 5 to 6 hours for polymer swelling. MXD was dissolved in measured quantity of solvents and this drug solution was added to the above polymeric solution. This step was followed by the addition of plasticizers such as PEG 400, Sweetener and flavour was also added. Constancy of drug content is reached by mixing in cyclo blender for 15-20 minutes. The solution was cast on a prepared mould and air dried for 45 minutes. The film was attentive removed from the mould.

Keywords: Moxonidine chloride, Orally Disintegrating Film, Drug efficiency

1. INTRODUCTION

Traditional oral solid dosage forms such as tablets, capsules are always preferred by patients over liquid dosage forms. Lifestyle and interest constantly evolving need more patient-friendly doses. Patient's disinterest in taking medicines which are difficult to

swallow resulted in origination of the concept of orally disintegrating solid dosage forms in 1970. When placed on the length of the tongue, it decreases in oral form to a suspension that is easily swallowed without water within a few seconds. Orally disintegrating systems like orally disintegrating tablets (ODTs), orally disintegrating films (ODFs) and wafers have carved nice amongst the oral drug delivery systems due to their high patient compliance **[1]**. MXD is a new generation of centrally acting antihypertensive drugs approved to treat mild to moderate critical hypertension. It may have a role in cases where ACE inhibitors, calcium channel blockers, beta-blockers and thiazides are not sufficient or have failed to regulate blood pressure.It also shows positive effects on parameters of insulin resistance syndrome, seemingly independent of the reduction of blood pressure.

It is manufactured by unichem Pharmaceuticals under the brand name Moxcent. MXD is a selective agonist at the receptor subtype-1. This type of receptor can be located in the rostral ventro-lateral and ventromedal depressor zones of the oblongate medulla. MXD therefore causes a decrease in sympathetic nervous system activity and therefore a decrease in blood pressure **[2]**. The major drawback of these conventional fast dispersing or dissolving tablets is their physicalsolid form. The fear of swallowing, chewing or choking on such solid shaped articles is still a concern in certain populations. In addition, the fragility / friability of wafer-like, porous and low-pressure moulded tablets created by various manufacturing processes, requiring special and costly packaging to secure dosage types, makes it difficult for patients, particularly children and the elderly, to bring, store, handle and administer them.To overcome the shortfalls of conventional fast dispersing or dissolving tablet Thin Oro Dissolving Film Technology has developed **[3]**. The film increases the risk of chocking / chocking terror, is easy to handle and administer, retains a clear and convenient packaging, relieves unpleasant taste, and is easy to make.

2. MATERIALS

MXD Gift sample is obtained fromunichem laboratories Ltd., Mumbai HPMC (Hydroxy propyl methyl cellulose) from Colorcon Asia Pvt.Ltd., Xanthan gum is obtained from Shilex Chemicals, Dichloro methane& Poly ethlylene glycol are obtained from S.D. Fine Chem Ltd., Mumbai. All other reagents and chemicals were of analytical grade and were purchased from S.D. Fine Chem Ltd.Mumbai. Purified water was used for study.

3.METHOD

3.1. Preformulation Study:

3.1.1. Drug - Polymer Compatibility Studies

An effective formulation of a safe and efficient solid dosage type relies on careful selection of excipients added to facilitate administration, promote the drug's consistent release and bioavailability and protect it from degradation. If the excipients are new and have not been used in the active substance containing formulation, compatibility tests are of utmost importance. Compatibility of MXD with the respective polymers that is HPMC, Xanthan Gum, and PEG 400 was established by Fourier Transform Infrared Absorption Spectral Analysis (FTIR).

3.1.2. Formulation of drug loaded films:

Oral Polymer films were prepared by solvent casting method. The ODF of MXD were prepared using HPMC E3, HPMC E6 and Xanthan gum. The polymer solution was prepared using a 1:1 mixture of dichloromethane and methanol and held aside for approximately 5 to 6 hours for polymer swelling was dissolved in measured quantity of solvents and this drug solution was added to the above polymeric solution. This step was followed by the addition of plasticizers such as PEG 400, Sweetenerand flavour was also added. Drug material uniformity is achieved by mixing for 15-20 minutes in a cyclo-mixer. The solution was cast for 45 minutes on a prepared mould and air dried. The film has been carefully removed from the mould, tested for imperfections and cut to the appropriate size to provide an equivalent dose(2x2cm2) per strip. Film samples with air bubbles, cuts, or imperfections were excluded from the study. Polymer films were prepared by solvent casting method according to the formula given in (**Table 1**) and prepared orally disintegrating films were shown in **(Figure 1).**

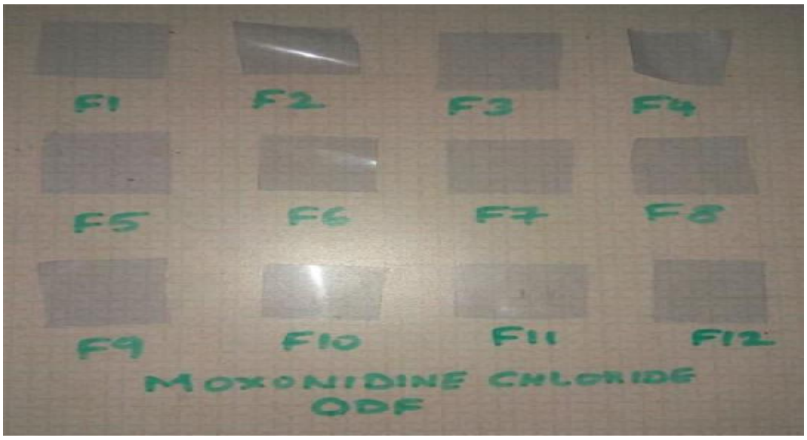

Figure 1: Orally Disintegrating films of MXD

Table 1: Formulation of Orally Disintegrating Films of MXD

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Moxonidine chloride	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
2	HPMC E3	100	200	300	--	--	--	--	--	--	--	--	100
3	HPMC E6	--	--	--	100	200	300	400					150
4	Xanthan gum	--	--	--	--	--	--	--	100	200	300	400	150
5	PEG 400	50	50	50	50	50	50	50	50	50	50	50	50
6	Aspartame	40	40	40	40	40	40	40	40	40	40	40	40
7	Orange Flavor	10	10	10	10	10	10	10	10	10	10	10	10

4.EVALUATION OF ODF'S:

a) Thickness measurement

Film should be measured at 5 positions i.e. centre and the 4 corners and the meanthickness are calculated. This test should be performed on six films of each formulation. It was expressed in mm.

b) Determination of moisture uptake

Films were cut into 2×2 cm square strips.The films' moisture uptake was determined by exhibiting them for one week to 75 percent relative humidity at room temperature.The uptakeof moisture by the films was measured and calculated as% increase in weight.

c) Tackiness evaluation

Tack is the persistence with which the film holds fast to an adornment that has been squeezed into contact with the film. The measurement of tackiness was carried out by gently pressing the film between the fingertips and qualitative results were reported as tacky or non-tacky **[4]**.

d) Film softening upon storage

Films have been processed in desiccators at room temperature for 48 hours. Films were then tested for softening and honesty.

e) Folding endurance

Folding endurance ismeasured by the number of folding times withoutbreaking the film.

f) In vitro disintegration time

In a glass petri dish containing 10 ml of distilled water, the film size needed for dose delivery (2x2 cm2) was put.It was noted that the time needed for the film to split was in vitro disintegration time.The research was carried out on triplets.

g) Drug content determination

Three samples of 1 cm2 surface area of film were cut and dissolved in 0.1 N HCl. Moxonidine hydrochloride concentration was estimated by UV-Visible spectrophotometer at 249 nm. Content uniformity should be within

85-115% and relative standard deviation should be not more than 6 %. Result shown in (**Table 2).**

h) In vitro dissolution study

The in-vitro dissolution study of prepared ODF formulations in USP type I (basket) using the Electro Lab dissolution rate test apparatus was carried out.ODFs of the desired formulation have been taken and placed in the vessels of the dissolution apparatus.Samples were obtained from vessels at various time periods, filled with the same amount of blank solution and analysed using the UV Vis spectrophotometer **[5]**. Drug concentration was calculated from the standard graph and expressed as % of drug dissolved or released. The release studies were performed in 6 replicates and mean values were taken. Result was shown in (**Table 3**) and (**Figure 3**)

Conditions for dissolution of MXD ODFs:

Apparatus	Labindia dissolution test apparatus (basket, modified USP I)
Medium	500 ml, 0.01 N HCl
RPM	50
Temperature	37 ± 0.5 ^{0} C
Sampling Volume	5 ml
Sampling intervals	5, 10, 15 and 20 minutes

i) Stability Studies:

A drug's stability has been defined as the ability of a specific formulation to remain within its physical, chemical, toxicological and therapeutic specifications in a particular container. In any rational design and evaluation of dosage forms for drugs, stability of the active component must be a major criterion in deter acceptance or rejection. The stability of a drug can be defined as the ability of a particular formulation to remain within its physical, chemical, toxicological and therapeutic specifications in a specific container. The stability of a drug may be described as the period from the date of manufacture and packaging of the formulation until its chemical or biological activity is no less than a predetermined degree of labelled potency and its physical characteristics have not significantly or deleteriously modified **[6]**. The International Conference on Harmonization (ICH) Guidelines titled ‘stability testing of New Drug substance and products**”** (QIA) describes the stability test requirements or drug registration applications in the European Union, Japan and the USA. ICH specifies the length of the study and storage conditions, result shown in (**Table 4**) and (**Figure 4)**

Long-Term Testing: 25°C ± 2°C / 60% RH ± 5% for 12 months.

5. RESULTS

5.1. Drug – excipient Compatibility Studies

The Drug excipient compatibility was ascertained by FTIR spectroscopy and the graphs were shownfrom (**Figure 2.1 to Figure 2.5**).

5.2 Evaluation of ODFs: (Table 2)

5.3 In vitro Dissolution Studies: (Table 3; Figure 3).

5.4 Stability Studies (Table 4; Figure 4).

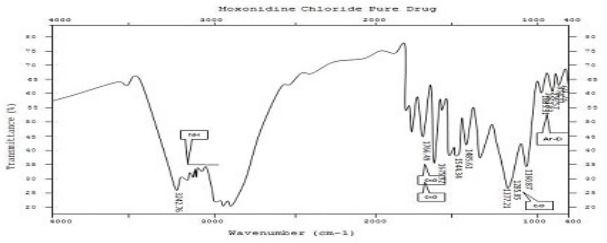

Figure 2.1 FTIR Spectrum of pure drug MXD

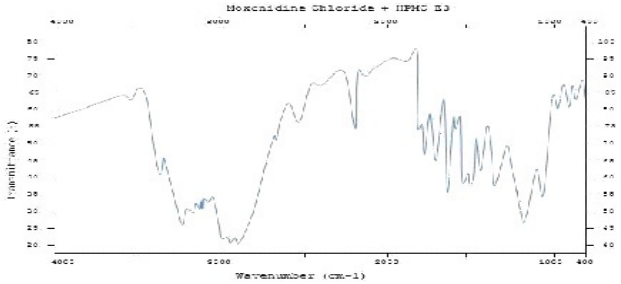

Figure 2.2 FTIR Spectrum of pure drug MXD + HPMC E3

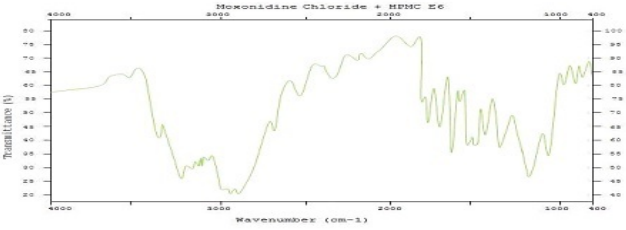

Figure 2.3 FTIR Spectrum of pure drug MXD + HPMC E6

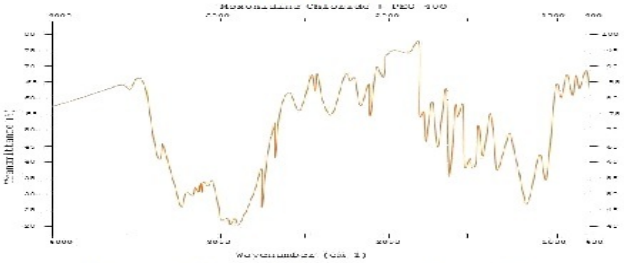

Figure 2.4 FTIR Spectrum of pure drug MXD+PEG400

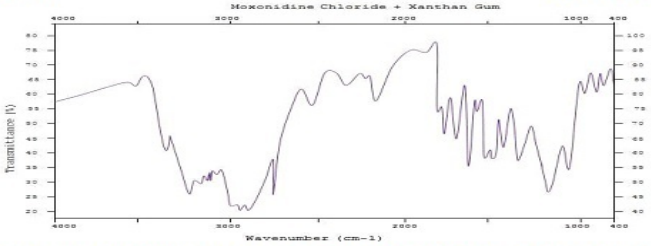

Figure 2.5. FTIR Spectrum of pure drug MXD + Xanthan Gum

Figure 2: FTIR Spectrum of Drug excipient compatibility

Table 2: The results of the evaluation parameters of Moxonidine Chloride ODF

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Film property	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Thickness	0.07	0.09	0.10	0.06	0.08	0.09	0.08	0.06	0.07	0.07	0.08	0.06
Folding endurance	25	12	23	18	15	13	23	29	33	12	31	11
Tackiness	Non tacky	Tacky	Non tacky	Non tacky	Non tacky	Tacky	Non tack	Non tack	Non tack	tacky	Non tacky	tacky
Disintegrating Time	30	25	29	28	30	26	29	25	30	25	25	23
Assay%	97.16	98.42	99.36	98.12	97.32	99.28	98.35	99.41	99.29	98.14	99.01	98.78

Table 3: %Cumulative Drug Release from ODF of MXD

TIME (Mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	40.51	50.42	28.72	39.33	37.11	49.17	48.42	38.61	41.25	51.47	43.8	62.2
10	66.12	77.91	46.33	64.18	66.09	75.41	63.91	64.34	53.9	78.9	71.2	84.4
15	84.31	92.89	61.92	82.19	80.36	90.35	78.71	81.90	71.54	93.55	89.7	98.7
20	92.63	98.97	77.81	90.07	96.17	98.76	84.62	90.14	89.56	99.26	92.5	--
30	99.17	--	89.02	98.84	--	--	92.87	98.71	98.74	--	98.6	--
45	--	--	98.04		--	--	99.03	--	--	--	--	--

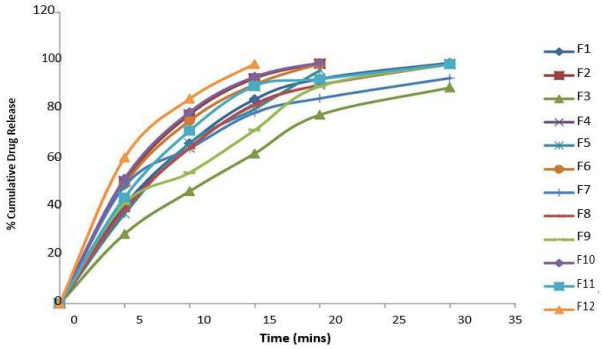

Figure 3: In vitro Drug Release of all the formulations

Table 4: Stability studies-Time Vs Drug Content

Time in Days	%Drug content in F12			
	RT	37°c/65%RH	45°/65%RH	40°c/75%RH
0	98.91	97.91	98.91	98.91
30	98.31	97.82	98.86	97.88
60	98.25	97.78	98.71	96.43
90	98.15	97.78	98.18	96.14

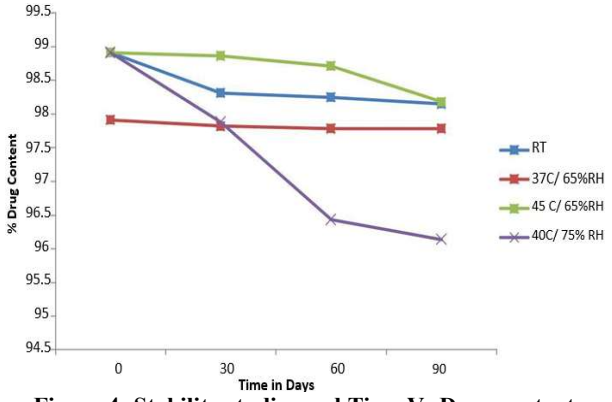

Figure 4: Stability studies and Time Vs Drug content

6 DISCUSSION

6.2 Drug – excipient Compatibility Studies

Compatibility studies of pure drug MXD with polymers were carried out prior to the preparation of tablets.IR spectra of pure drug MXD and that with excipients were obtained, which are depicted. All the characteristic peaks of MXD, 3242.76 cm^{-1}(-NH),1766.49 cm^{-1},1675.92 cm^{-1}(C=O),1285.05cm^{-1}(C-O)And 1061.83 cm^{-1}(Ar-Cl) were present in the spectra at respective wavelengths, indicates compatibility between drug and

excipients.It shows that there was no significant change in the chemical integrity of the drug.

6.3 In vitro Dissolution Studies:

The in vitro dissolution studies were carried out in 6.8 pH phosphate buffer using Type I USP basket apparatus. F2 containing HPMC E3 released 98.97% drug in 20 mins, F6 containing HPMC E6 released 98.76% drug n 20 mins, F10 containing Xanthan released 99.26% in 20 mins. Finally, the formulation F12 containing half the optimized concentrations of HPMC E3, E6 and Xanthan gum released 98.76% drug in just 15 mins. Hence it is chosen as the best formulation.

6.4 Stability Studies:

Stability studies were carried out for best formulation F12 at Room temperature, 37^0C/65% RH, 45^0C/65% RH and 40^0C/75% RH according to ICH guidelines. The % drug content was analysed at 0,30,60 and 90 days which are within the acceptance criteria of 95-105%. Thus, the formulation is found to be stable.

7 SUMMARY:

FTIR study shows no drug-excipient interaction. The orally disintegrating films (ODF) were prepared by using solvent casting technique with water soluble polymers like HPMC E3, HPMC E6 and Pullulan gum of various concentrations and PEG 400 as a plasticizer and an active ingredient, MXD is used to measure the effect on dissolution profile. The results shown that drug dissolved quickly. This study indicates the possibility of oral delivery of MXD by orally disintegrating film.The dissolution of ODF formulations released complete drug within 20-30 minutes and are smooth and easy to swallow. No residue and particulate matter were left after disintegration. ODF formulations prepared with HPMC E3 in the concentration of 100mg, 200mg and 300mg. Among them, the films prepared with 200mg concentration (F2) was found to be best formulation. Further increase in concentration (300mg-F4) delayed the drug release. ODF formulations prepared with HPMC E6 in ratios of 100mg, 200mg, 300mg and 400mg. Among them, the films prepared with 300 mg concentration (F6) was found to be best formulations. ODF formulations prepared with Xanthan gum in ratios of 100mg, 200mg, 300mg and 400mg. Among them the films prepared with 300 mg concentration (F10) was found to be best formulations. So, a formulation containing half the concentrations of the individual polymers was developed F12, which has better properties and more effective drug release within 15 mins.

8 CONCLUSION

It was concluded that the fast dissolving films of MXD were successfully prepared by solvent

casting technique ODFwere successfully employed to the bedridden and psychotic patients and travelling persons where there is no access of water. Prepared films showed enhanced dissolution rate, with rapid onset of action, and hence better patient compliance, effective therapy and its popularity in the near future.

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Conflict of interest

The authors declare that they have no conflict of interest. The article does not contain any studies with animals or human participants performed by any of the authors.

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