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Research

Formulation And Assessment Of Oral Disintegrating Films Containing Doxazosin Mesylate

Mohd. Adil Hussain*, K. Tharun kumar[1], T. Sowmya[2], Dr. T. Mangilal[3], Afreen Banu[4]

Smt.Sarojini Ramulamma College Of Pharmacy, Seshadrinagar, Mahabubnagar, Telangana – 509 001, India

*Author for Correspondence: Mohd. Adil Hussain
Email: teelavath@gmail.com

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Abstract

The medication's efficacy and safety profile may be enhanced, dosage may be decreased, and the onset of action may be accelerated with oral disintegrating films. Compared to other conventional dose forms, it dissolves more quickly, is more stable, and has a longer half-life. Doxazosin mesylate (DXZ) was selected for the sublingual route in order to produce fast-dissolving films that dissolves in saliva quickly and without the need for water. The influence on the dissolution profile is measured using DXZ. The solvent casting method was used to create the oral disintegrating films (ODF), which contained PEG 400 as plasticiser along with water-soluble polymers such as HPMC E5, HPMC E15, and locust bean gum in different quantities. The results showed that the medicine vanished quickly. Data showed the DM9 dissolved quickly, releases 99.96 drug in 20 min. This study advises giving DXZ orally with a film that dissolves when ingested. DM3 (HPMC E5) disintegrates in 19 seconds, and DM6 (HPMC E15) in 21 seconds. As compare to synthetic polymer, natural polymer locust bean gum disintegrates within 9 seconds only. No particles were discovered after disintegration. Based on disintegration time and dissolving trials, it was concluded that DM9 was the best formulation.

Keywords: Orally disintegrating films, Doxazosin mesylate, Locust bean gum, HPMC E5, HPMC E15, Solvent casting method

INTRODUCTION

Orally disintegrating tablets and Oro dissolving films are two of the fast-dissolving medication delivery technologies that have been developed as alternatives to traditional dose forms in order to help these individuals. Because oral medicine delivery has the highest compliance rate, especially among pediatric and geriatric patients, it is considered the most practical, affordable, and safest drug delivery method. Any medication delivery system's

ultimate purpose is to successfully deliver the drug to the body. Among the different dosage forms, the oral disintegrating dosage form is the most popular commercial product[1]. The film decreases the risk of choking and the fear of choking, is simple to make, easy to handle and administer, and has handy packaging. It also lessens the taste that is unpleasant. These thin polymer films are also known as melt-in-mouth dosage forms (MDF), mouth dissolving films (ODF), quick dissolving films (QDF), rapidly dissolving films (RDF), and oral dissolving films (ODF)[2].

Some formulations were developed earlier that are atorvastatin[3], zolmitriptan[4], levocetrizine dihydrocloride[5], amlodipine besylate[6], ondansetron[7], promethazine hydrochloride[8], risperidone[9].DXZ is antihypertensive drug which is crystalline powder that ranges from white to off-white. Highly soluble in water (0.8 percent at 25 °C), methanol, and ethanol; very weakly soluble in acetone and methylene chloride; and readily soluble in dimethylsulfoxide and dimethylformamide. Doxazosin blocks alpha1-adrenergic receptors, causing peripheral vasodilation. This lowers peripheral vascular resistance and lowers blood pressure[10]. To be best of our knowledge ODFs of DXZ with natural polymer locust bean gum; HPMC E5 and HPMC E15 were not found in the literature. Therefore, the present research has been initiated.

MATERIALS & METHODS

Chemicals

Doxazosin mesylate obtained as a gift sample from UniChem laboratories Ltd., Mumbai. Locust bean gum is purchased from Shilex Chemicals Pvt. Ltd., Delhi. HPMC, PEG 400 and citric acid were purchased from S.D. Fine-Chem Ltd, Mumbai. Chocolate flavour was purchased from Pentagon trading company, Mumbai.

Calibration of DXZ

To a 100 millilitre volumetric flask, 100 milligrammes of carefully weighed DXZ are introduced. The volume was raised to 100 ml using a stock solution of 1 mg/ml of 6.8 pH phosphate buffer. The stock solution was diluted to obtain solutions with concentrations of 5, 10, 15, 20, 25, and 30 µg/ml using 6.8 pH phosphate buffer (0.5, 1, 1.5, 2, 2.5, and 3 ml stock solution are diluted with 100 ml buffer). A UV-VIS spectrophotometer (EI 1372, Electronics India, Pune, India) phosphate buffer blank 6.8 pH was used to quantify these solution's absorbance using a standard graph at wavelenth 245 nm.

Drug - Polymer Compatibility Studies (FTIR)

An FTIR study was carried out to ascertain whether the drug and polymers were compatible. The infrared spectra of DXZ were recognised using the ATR FTIR spectrometer (Shimadzu FTIR-8400S, Japan). The mid-IR 4000-400 cm-1 spectral range was covered by the diffuse reflectance approach. The process entails utilizing a motor to disperse the sample in KBr (100 mg), then a compression gauge to triturate the materials into a fine powder bed inside the holder. For five minutes, the pressure was about five tons. The pellet was positioned along the light path, the spectrum was captured twice, and the distinctive peaks of the functional groups were deciphered.

Formulation Design[11]:

A natural polymer known as locust bean gum and several grades of Hydroxy Propyl Methyl Cellulose, including HPMC E5 and HPMC E15, were used to create DXZ ODFs using the solvent casting method. Doxazosin dose is 4mg for each film.

Table 1: Formulation table of Doxazosin mesylate ODF

Ingredients (mg)	DM1	DM2	DM3	DM4	DM5	DM6	DM7	DM8	DM9
Doxazosin mesylate (For 25 films)	100	100	100	100	100	100	100	100	100
HPMC E5	80	160	240	-	-	-	-	-	-
HPMC E15	-	-	-	80	100	120	-	-	-
Locust bean Gum	-	-	-	-	-	-	240	320	400
PEG 400	0.8	1.6	2.4	0.8	1	1.2	2.4	3.2	4
Citric acid	5	5	5	5	5	5	5	5	5
Sod. Sachharine	4	4	4	4	4	4	4	4	4
Chocolate Flavor	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

**The above formulation was calculated for 25 films of 2x2 cm size.*

Preparation of ODF

We employed the solvent casting method to make doxazosin (DXZ) ODF. The ODF of DXZ was produced using locust bean gum, HPMC E5, and HPMC E15. The polymer was then allowed to expand for five to six hours. The drug solution had been added to the previously described polymeric solution. Next was the addition of plasticisers, like PEG 400. Citric acid as saliva stimulating agent; sweetener and chocolate flavour were also added. Mixing in a cyclo mixer about 15 to 20 minutes will homogenise the drug content. A two-hour magnetic stirrer stirs the solution to expel all air bubbles, then it is left. The solution is then cast in a square glass plate (10 cm x 10 cm x 1.7 cm, Othmro, Amazon, India) and air-dried overnight to form a film. The dried film was carefully removed from the mould, inspected for faults, and trimmed to the specific size (2x2 cm2) for each strip. The investigation excluded film samples with cuts, air bubbles, or other problems.

Evaluation of oral disintegrating films formulations:

Thickness measurement[12]

The film's thickness was measured five times using a micrometer screw gauge, and an average of three readings was determined.

Weight variation[13]

Using an analytical balance, the average weight was calculated for each film.

Folding endurance[14]

The value of folding endurance is determined by the number of times the film could be folded in the same way without breaking.

Drug content uniformity

By evaluating the API content in each individual strip, content consistency is ascertained. 85–115% is the maximum content homogeneity[15].

Surface pH

The film that was going to be tested was put in a Petri dish, wet with 0.5 milliliters of distilled water, and left for thirty seconds. After allowing one minute for equilibration and contacting the formulation's surface with the pH meter's electrode, the pH was recorded. For every formulation, an average of three determinations was made[16]

Assay

One film, chosen at random from the five, was weighed, then added to 100 milliliters of 6.8 pH buffer in a volumetric flask. For thirty minutes, a volumetric flask was submerged in a sonicator. The finished solution's absorbance was measured at 245 nm utilising a UV Visible spectrophotometer against a 6.8 pH buffer blank. Concentrations and formulation amount were calculated using a standard graph.

Tensile strength[17]

The greatest stress applied to the point at which the strip specimen breaks is known as its tensile strength.

***In vivo* disintegration studies**

Disintegration test equipment was used. Disintegration time indicates film disintegration and decomposition. In a stainless steel wire mesh with 25 ml of pH 6.8 simulated salivary fluids, place the desired film size (2x2 cm^2). The time it takes the film to dissolve is called disintegration time[18].

***In vitro* Dissolution test**[19]

An in-vitro dissolving analysis of the created ODF formulations was conducted using EI -1916, Electronics India, Pune, India; USP type I dissolution test instrument (basket). Drug concentration was determined using the standard graph and reported as a percentage of the drug that was released or dissolved. The release studies were conducted in six duplicates, and mean values were noted.

Release Kinetics[20]

The findings from the invitro diffusion investigation were used to investigate the order and mechanism of drug release kinetics of DXZ films. The kinetic models that were plotted included the zero order, first order, and Higuchi equations; the release was calculated using the Korsmeyer-Peppas equations.

Stability Studies

The designated formulations were tagged and placed in strip packing with aluminium foil in polyethylene packets. After that, they were kept at 40°C/75% RH. Maintained for three months and assessed, in accordance with ICH Guidelines, for their appearance, medication content, and drug release at predetermined intervals[21].

RESULTS & DISCUSSION

Calibration of DXZ

Combine 50 mg of DXZ in 100 ml of water to get the stock solution. To make 100 millilitres, 10 millilitres of the stock solution were removed and diluted with water. Using several concentrations (2–10 µg/ml) and the appropriate stock solution dilution, a calibration curve was produced. The absorbance was obtained at 245 nm. The curve that results from calibrating DXZ in a pH 6.8 phosphate buffer is shown in Figure 1.

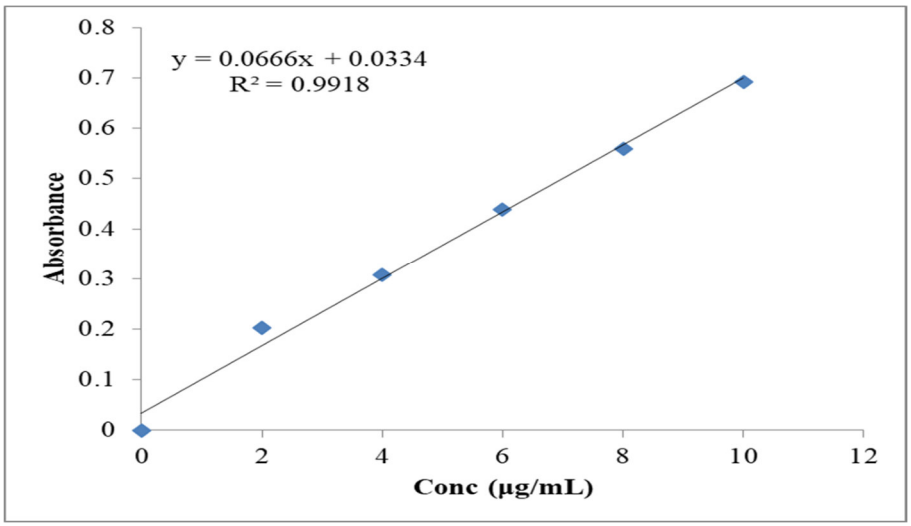

Fig 1: DXZ standard calibration curve in phosphate buffer with a pH of 6.8

Drug – excipient Compatibility Studies

FTIR spectroscopy was used to determine the drug excipient compatibility, and the graphs from the figure were displayed. To find out if there is any interaction between the excipients and DXZ, the physical mixture was put through FTIR analysis. The lack of a drug-carrier chemical interaction is confirmed by the absence of any drug-characteristic peak appearance or disappearance. All samples, which were pure DXZ, underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

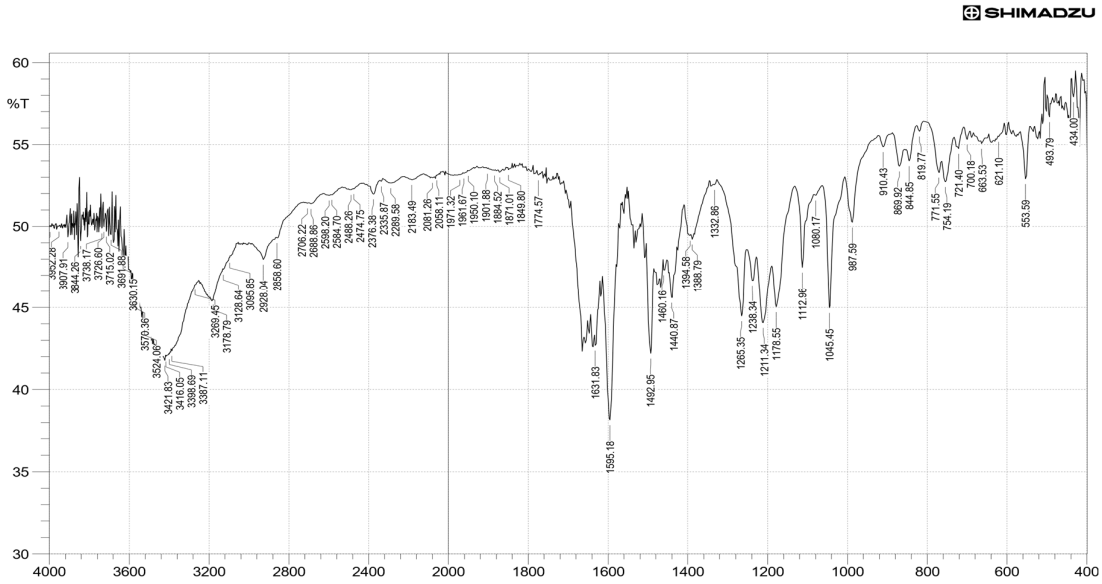

Fig 2: FTIR Spectral analysis of pure DXZ.

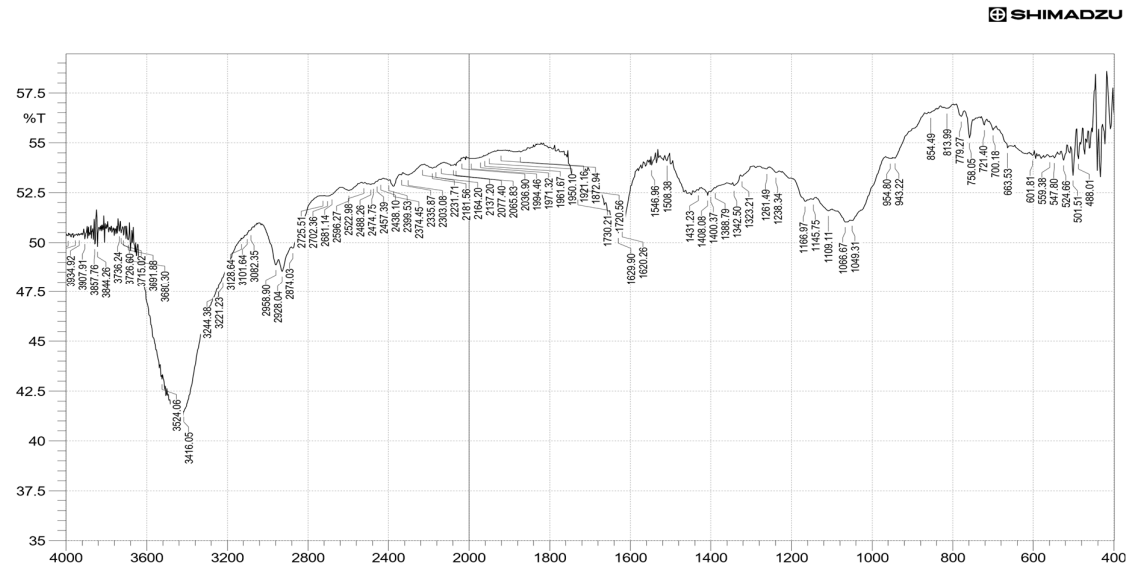

Fig 3: FTIR Spectral analysis of optimized formulation.

Distinct peak in the region 2982-2862 cm
-1
for C-H aliphatic, 1350-
1000 cm
-1
for C-N amine and 3500-3100 cm
-1
secondary amine,
3450-3300 cm
-1
for N-H group, 3200-3000 cm
-1
for = C-H group and
1900-1600 cm
-1
for C=O group was identical to that off which confirm the compatibility of the drug and carrier. The spectra are shown in fig. 2 for pure DM, PEG 8000 and DM-PEG 8000 solid dispersion respectively.

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shown in fig. 2 for pure DM, PEG 8000 and DM-PEG 8000 solid
dispersion respectively.
The obtained FTIR spectra are superimposed in the figure 2-3. The spectrum clearly shows the primary characteristic bands associated with pure DXZ, and the data are in line with the scientific literature. The principal peaks for N-H stretching were found at 3178.79 cm−3, C=N stretching at 1492.95 cm−3, C-N stretching at 1265.35 cm−3 and C=O stretching at 1178.55 and 1045.45 cm−3. There was no interaction, based on the observed absorption peaks of the drug and excipients.
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Distinct re

ODF formulation

ODF formulations DM1-DM3, with concentrations ranging from 80 to 240 mg, are produced using HPMC E5. ODF formulations DM4-DM6 are made with HPMC E15 at doses between 80 and 120 mg. ODF formulations DM7-DM9 are made with a natural polymer, locust bean gum at 240-400 mg dosages. As compare to synthetic polymers HPMC E5 and E15, the natural polymer locust bean gum showed lesser disintegration time of 9 sec. It was found that the films with the optimum formulation was produced with a 400 mg concentration (DM9).

Evaluation of ODF

The findings are displayed in the table 2. DM1–DM9 were determined to be 91.43±0.61–111.51±0.38µm thick. It was discovered that the folding endurance value of DM1–DM9 was 119±9-186±4. The surface pH of each film ranged from 6-7. The disintegration time for DM1–DM9 was found to be in between 9±2-27±3 seconds.

Table 2: Finding the thickness, folding endurance, and pH of the surface and disintegration time of all formulations

F. Code	Thickness (µm)± SD	Folding endurance (Folds)	Surface pH	In-vitro disintegration Time (sec)
DM 1	91.43±0.61	128±6	6.09±0.12	25±4
DM 2	101.28±0.57	122±5	6.21±0.13	22±4
DM 3	105.63±0.36	119±9	6.16±0.09	19±2
DM 4	97.21±0.29	151±3	6.18±0.11	27±3
DM 5	104.18±0.39	144±6	6.11±0.08	24±4
DM 6	109.32±0.68	138±7	6.09±0.12	21±2
DM 7	98.42±0.58	158±11	6.22±0.19	22±3
DM 8	106.38±0.47	165±8	6.29±0.13	16±4
DM 9	111.51±0.38	186±4	6.22±0.09	9±2

Table 3 shows the results of DXZ ODF's weight variation, drug content uniformity, and assay determination. Weight variance varies between 48.26±0.16-58.32±0.24. DM9 was found to be the best having a drug content percentage of 103.44±2.21. The assay findings for each formulation ranging in between 95.51±2.95-99.91±3.35%.

Table 3: Weight variation, drug content uniformity, and assay determination

F. Code	Weight variation	Drug Content Uniformity	Assay
DM 1	48.26±0.16	94.45±2.17	96.26±3.33
DM 2	50.19±0.36	95.16±3.27	95.51±2.95
DM 3	52.21±0.28	96.28±2.48	98.29±4.82
DM 4	51.74±0.21	103.33±4.13	96.12±5.47
DM 5	53.28±0.34	105.53±6.12	96.48±3.72
DM 6	54.32±0.42	108.42±3.26	98.54±4.62
DM 7	55.86±0.36	98.42±5.16	97.71±4.34
DM 8	57.29±0.21	101.28±4.23	98.46±5.52
DM 9	58.32±0.24	103.43±2.21	99.91±3.35

In-vitro dissolution

For DM1-DM9, figure 4 displays the cumulative medication release percentage. Utilizing a Type I USP basket apparatus, the in vitro dissolution investigations were conducted in phosphate buffer with a 6.8 pH. In 20 minutes, DM3 with HPMC E5 released 95.05% of the drug; DM6 with HPMC E15 released 97.29% and DM9 with locust bean gum released 99.96%. As a result, it is regarded as the ideal formulation.

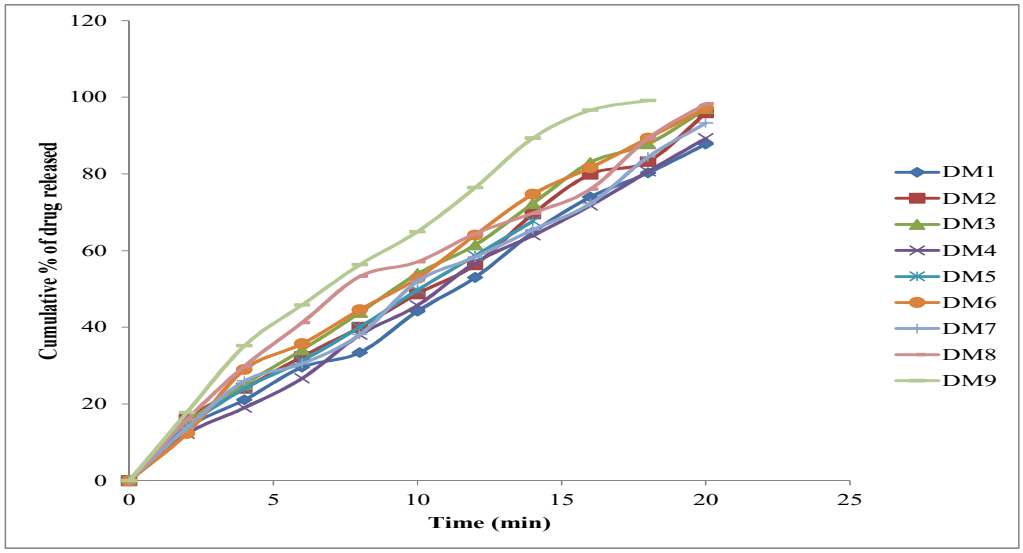

Fig 4: Invitro dissolution studies of formulations (DM1-DM9)

Application of Release Rate Kinetics to Dissolution Data:

The kinetics of drug release were investigated using a range of models. The drug release rate mechanism of the dose form kinetics was examined by fitting a variety of release models, such as first-order, zero-order, higuchi, and Korsmeyer-Peppas, to the collected data.

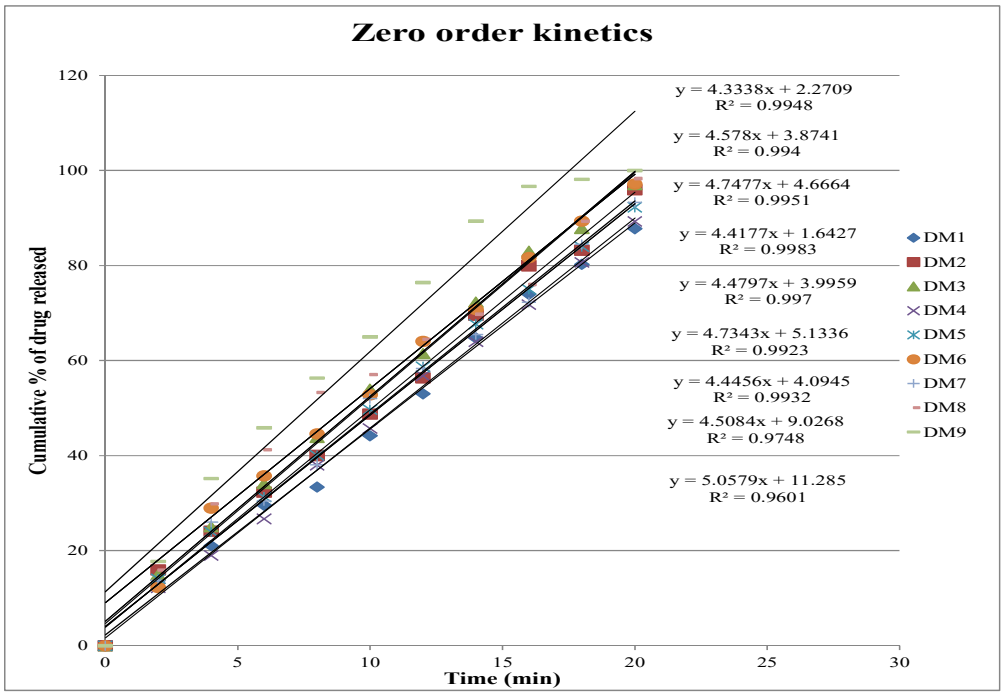

Fig 5: Zero order release kinetics graph of DXZ formulations (DM1-DM9)

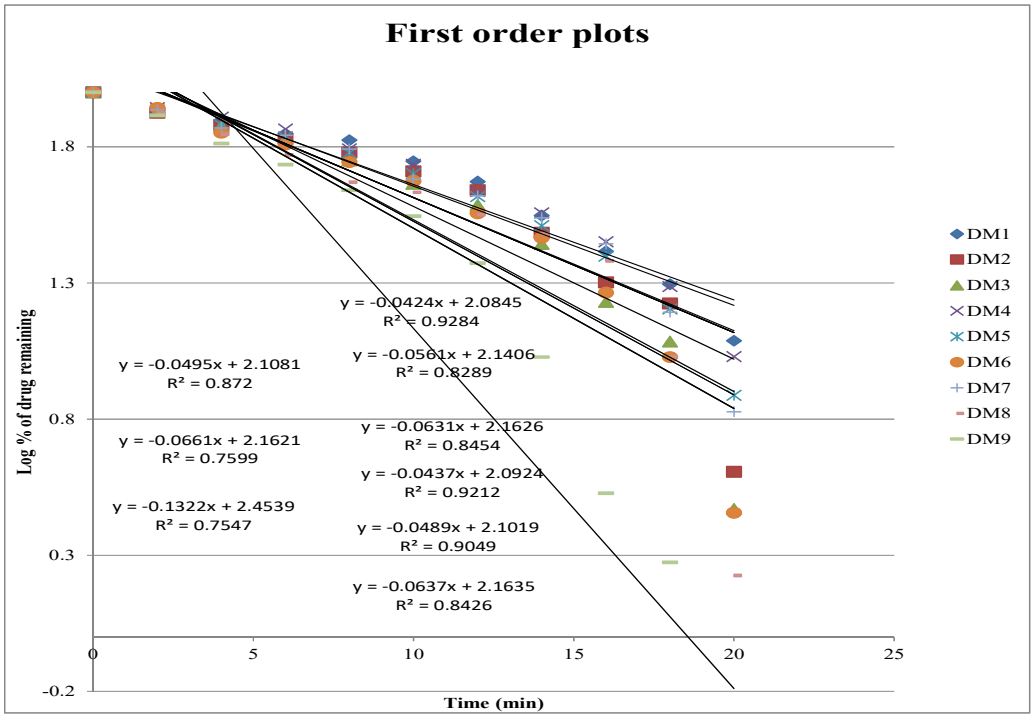

Fig 6: First order release kinetics graph of DXZ formulations (DM1-DM9)

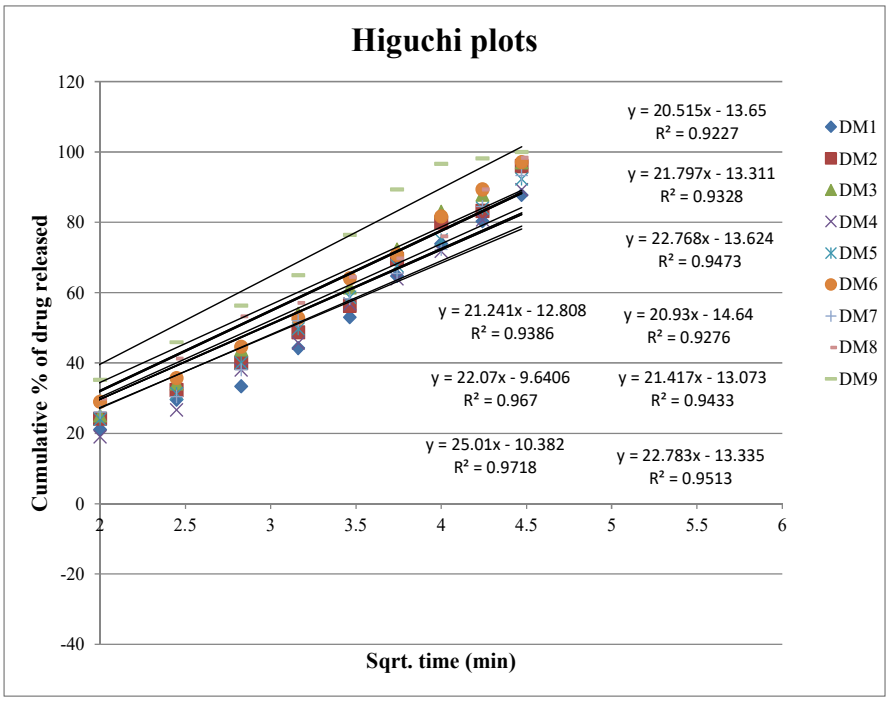

Fig 7: Higuchi release kinetics graph of DXZ formulations (DM1-DM9)

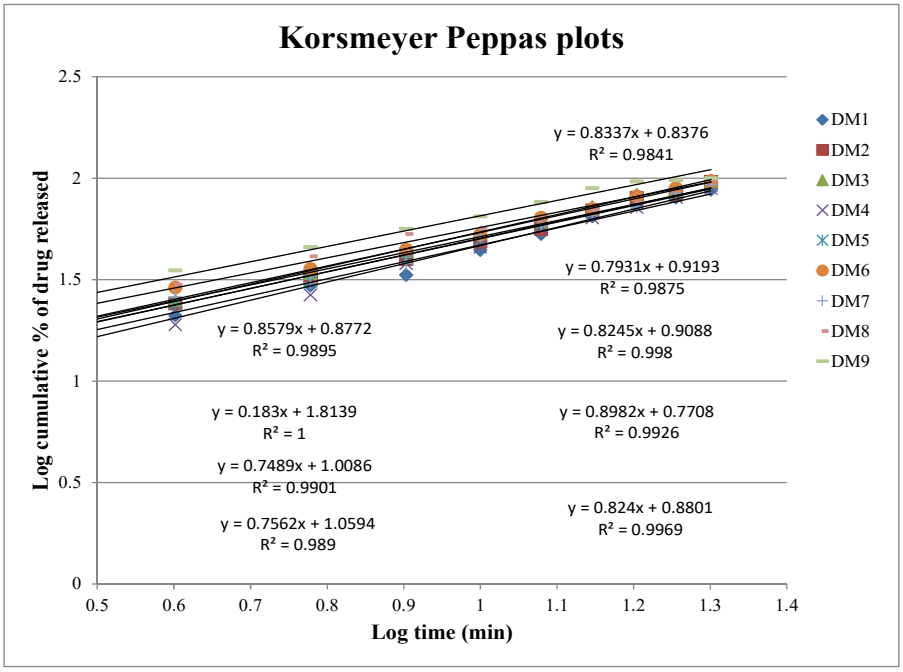

Fig 8: Korsmeyer-Peppas graph of DXZ formulations (DM1-DM9)

The drug release kinetics are summarized in Figure. 5 to 8 and indicated that DXZ followed zero order release from all the formulations (R^2 0.9601 to 0.9983). It is further noted that all the formulations followed diffusion mechanism of drug release (R^2 >0.6705), and specially formulations DM9 which had R^2 of 0.9718 respectively. Koresmeyer peppas equation determines the drug transport mechanism based on the values of coefficient 'n'. If n=0.5 it is Fickian, if n=0.45 to 0.89 then non-Fickian transport, if n=0.89 it is Case II transport, and if >0.89 it is Super case transport. The 'n' value obtained for DM9 was 0.7562 respectively, which indicate that the drug

transport mechanism from the DXZ was non Fickian.[22]

Stability Studies

In accordance with ICH requirements, stability experiment was conducted for the optimal formulation of DM9 at room temperature, 40^0C/75%RH. The drug content percentage was examined at 0, 30, 60, and 90 days, all of which fall within the 95–105% acceptability range. It follows that the formulation is stable.

CONCLUSION

The solvent casting method was found to be successful in creating the DXZ films that dissolve quickly. Orally disintegrating films (ODF) have proven to be a successful treatment for patients who are psychotic, bedridden, or travelling in places without water. DXZ films were subjected to quality control testing, which included in-vitro diffusion, kinetic and stability investigations, disintegration time, surface pH, folding endurance, thickness, and weight variation. The optimised formulation, DM9, was stabilized at accelerated stability conditions. As a result of prepared film's enhanced dissolving rate and rapid onset of action, patient compliance improved, therapy was successful, and their popularity grew in the near future.

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