International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (4): 122-129
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Biological Sciences | Open Access | MCI Approved

Formulation and Evaluation of Taste Masked Oro-Dispersible Dapoxetine Hydrochloride Tablet

Vishal S. Gujare and Avinash B. Gangurde
Department of Pharmaceutics, K.B.H.S.S Trust's Institute of Pharmacy, Malegaon, Nashik District, Maharastra-423203, India

Received: 02 Jul 2019 / Accepted: 12 Aug 2019 / Published online: 1 Oct 2019
***Corresponding Author Email:** vishalgujare95@gmail.com

Abstract
To developed Oro-dispersible tablet of Dapoxetine hydrochloride for premature Ejaculation treatment.The bitter taste of drug should be masked in order to formulate in luscious form. Taste masked of bitter taste of Dapoxetine hydrochloride by solid dispersion technique. The prepared by solid dispersion of Dapoxetine hydrochloride with Eudragit E-100 in various drug:complex ratio, formulation in to Orodispersible tablet, using superdisintegrants SSG, CP, CCS in different concentration. Oro-dispersible tablet was formulated and evaluated of thickness, weight variation, hardness, friability, drug contain, wetting time, water absorbtion ratio, In-vitro release time and disintegration time. Dapoxetine hydrochloride and excipients used in study were found compatible. fast dissolving taste masked Oro-dispersible tablet of Dapoxetine hydrochloride was successfully develop. Among three developed solid dispersion Dapoxetine hydrochloride: Eudragit E-100 (1:1) was possessed no disagreeable taste. Among developed nine formulation of Dapoxetine hydrochloride solid dispersion (1:1), formulation-F6 contain crosspovidone released 98.36±1.26% drug within nine min. which was found as best formulation.

Keywords
Dapoxetine hydrochloride, Oro-dispersible tablet, Eudragit E-100, Taste masking, Premature Ejaculation

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INTRODUCTION
Oro-dispersible tablet is solid unit dosage form like a conventional tablet. Composed of super disintegrants excipient which help them to dissolved tablet within a 1 minute in a mouth cavity in the presence of saliva. When put in the mouth, these dosage form disintegrate rapidly to release the drug in disperses in saliva. There after they may get absorbed from pharynx and oesophagus of gas in the digestive track as saliva travels to down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage from [1,2].

Ejaculation
Is the sudden, pleasurable release of semen through the penis. It is controlled by your brain (your central nervous system). When you are sexually stimulated, signals are sent of spinal cord to brain. When high a certain level of sexual excitement your brain tells

your reproductive organs to go this causes semen to flow out through the penis [3].

Premature Ejaculation

Ejaculation is a nearly always occurs prior to flow semen one minute of vaginal penetration, and negative personal consequences of sexual in time. Premature Ejaculation is ejaculation that starts sooner than a man wants. It can happen before or shortly after penetration (intercourse). Other names for this are rapid Ejaculation, Early Ejaculation.

Two types of premature ejaculation

a) Lifelong (primary)

b) Acquired (secondary) [3]

MATERIALS AND METHODS

Materials

Dapoxetine hydrochloride was obtained as a purchased from Ajanta pharma Aurangabad, India and Eudragit E-100 was purchased from Evonic pharma, India. Maize starch, crospovidone, PVPK-15, magnesium stearate was obtained pallav chemical. Maicrocrystalline cellulose, sodium starch glycolate, crosscarmellose sodium, talc was received from Vishal chemical.

Methods

Drug excipients compatibility study

FTIR studies were carried for the Dapoxetine hydrochloride and Oro-dispersible formulation containing Eudragit E-100, maize starch, microcrystalline cellulose, Sodium starch glycolate, crospovidone, croscarmellose sodium, polyvinylpyrrolidone, magnesium stearate, talc, mannitol using FTIR spectrophotometer (Agilent technology), over the wave number range 4000-400 cm-1. The study was performed to interpret drug excipients compatibility.

Preparation taste masking of Dapoxetine hydrochloride

Total three solid dispersion of Dapoxetine hydrochloride with Eudragit E-100 (1:0.5, 1:0.75, 1:1 molar ratios) was prepared by solid dispersion methods. The drug was dissolved in ethanol. Eudragit E-100 dissolved in sufficient quantity ethanol. Then both solutions mix slowly. After at room temp the solvent was evaporated. Finally, the obtain crystalline powder was sived through #80 sieve and stored in desiccators. The physical mixtures of Dapoxetine hydrochloride and Eudragit E-100 as like 1:0.5, 1:0.75, 1:1 molar ratio was also prepared and mixing by using mortar and pestle.

Evaluation of taste masking study

The sample of solid dispersion to sensory evaluation by a use three volunteers. the volunteers were asked to compare the bitterness of each ratio the class of bitterness perceived by them. The volunteers were asked to gargle and wait for 30 min and after another sample was to give for taste evaluation. Evaluation taste masked are shown in Table:1

Table 1 Evaluation of taste masking study

Solid dispersion	Taste masking class			Inference
	A volunteer	B volunteer	C volunteer	
DH:EE100 (1:05)	2	3	2	Slightly disagreeable
DH:EE100 (1:75)	2	2	2	Slightly disagreeable
DH:EE100 (1:1)	1	1	1	No disagreeable
DH	3	3	3	Moderate

(DH:EE100 means solid dispersion of Dapoxetine hydrochloride and Eudragit E100, DH means Dapoxetine hydrochloride)

The taste masked of solid dispersion was found ratio of 1:05 in class 2 Slightly disagreeable, 1:75 in class 2 Slightly disagreeable and ratio of 1:1 was no disagreeable. So, the ratio of use best for Oro-dispersible Dapoxetine hydrochloride formulation.

Formulation of Dapoxetine hydrochloride Oro-dispersible tablet

Tablets consisting of 54 mg solid dispersion complex (1:1 molar ratio) drug using equivalent to 25 mg different concentration of superdisintegrant as like sodium starch glycolate, crosspvidone and croscarmellose sodium. As well as use excipients of maize starch, microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate, talc and mannitol. The drug solid dispersion, excipients, sweetener, flavor and superdisintegrants was passed through #80 sieve. After all the ingredients was properly mixed in polybag. Talc and magnesium stearate were passed through #80 sieve and then blended with the mixture of in polybag. Finally, the powder blend obtained were compressed into tablets on a 7-station rotary tablet punch. Developed formulation are shown in table 2.

Table 2 Formulation table of Dapoxetine hydrochloride Oro-dispersible tablet

Ingredients	Quantity (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
SD (1:1 molar ratio) of Dapoxetine hydrochloride	54	54	54	54	54	54	54	54	54
Maize Starch	34.5	27.0	19.5	34.5	27.0	19.5	34.5	27.0	19.5
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30
Sodium starch glycolate	7.5	15.0	22.5	-	-	-	-	-	-
Crospovidone	-	-	-	7.5	15.0	22.5	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	7.5	15.0	22.5
PVPK-15	6	6	6	6	6	6	6	6	6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Manitol	15	15	15	15	15	15	15	15	15

Evaluation of pre-compression parameters

Flow properties of blended powder [6]

Angle of repose

The powder of mixture allowed through the funnel fixed to a stand at definite hight (h). The angle of repose
was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. This explains relationship between angle of repose and powder flow properties.

Formula:

$$\theta \tan^{-1}\frac{h}{r}$$

Bulk densities of the blended powder

It's ratio of total mass of powder to bulk volume of powder was measured by pouring the weight powder in
to a measuring cylinder and initials weight was noted. This initial volume is called the bulk volume. From this, bulk density was calculated according to the formula mentioned below. It's expressed in g/mol.

Formula:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Volume of powder}}$$

Tapped densities of the blended powder

It's ratio of total mass of the powder to tapped volume of powder. Volume was measured by100 time taping
of powder and tapped volume was noted. If the different between these two volumes is less than 2%.

Formula

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{volume of powder}}$$

Hausner's quotient

Hausner's ratio is indirect index of powder flow. It's calculated by following formula

$$\text{Hausner's quotient} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's compressibility index

It's indicates flow property of powders is expressed in percentage.

Formula:

$$\text{Carr's compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} X100$$

Evaluation of Oro-dispersible Dapoxetine hydrochloride formulation

Thickness

Randomly taken from each formulation twenty tablets and there was measured thickness by using Vernier callipers. The mean ± S.D. value was noted. Thickness of tablet must be within a ±5% variation of standard value

Weight variation

The weight of individual tablet was calculated and campared with the average weight. The mean ±SD was noted the tablets meet United states pharmacopoeia (USP) specification not more than two tablets out of present limit

Diameter

The individual tablet of diameter measured with a digital vernier caliper, which permits accurate measurements and provides information on the variation between in tablet

Hardness

Hardness is force of required to break a tablet in a diametric compression. The hardness of tablet from various formulation was measured using pfizer hardness tester and expressed in kg/cm2 a minimum hardness is 4kg is acceptable for Oro-dispersible tablet.

Friability

Friability of tablets determined by using roche fribilator. This apertures tablet to combined effect of abrasion and shock in plastic chamber revolving at 25

rpm and dropping a tablet from a height of 6 inches in each revolution. Before weight of 10 tablets was placed in plastic chamber friabiltor attached to a motor and subjected a 100 revolution. The total tablet after subjection to friability teste were dedusted using a soft muslim colth and the reweight present loss of tablet weight was calculated. This formula of friability was given below Formula:

$$\%\text{Friability}=\frac{W1-W2}{W1}X100$$

W1= Initial weight of tablet

W2= Final weight of tablet

Uniformity of Drug content

Randomly five tablets were selected each formulation batch and prepared powder by using mortal and pestel.

The amount of powder take equivalent to average weight after was added 100ml phosphate buffer, pH 6.8 in

a conical flask. Then conical flask on a rotary shaker and aliquot of the solution was subjected to centrifugation and the supernatant were filtered through a 0.22µ filter then absorbance of the resultant Supernatant solution was measured using UV- visible spectrophotometer at **λ** max of 230 nm with phosphate buffer, pH 6.8 as a blank. Finally, the concentration was calculated with the help of standard graph and total amount of drug present in the formulation was determined.

Wetting Test

Take a small Petri dish in six ml of water, a small piece of tissue paper folded twice and kept in Petri dish. To the Petri dish, a water-soluble phenolphthalein dye was added. Then dye solution was used identification of complete wetting of tablet surface. A tablet from each formulation batch were placed carefully on the surface of folded tissue paper in Petri dish at room temp. The time taken for water to reach the upper surface of tablets and fully wet after was noted as the wetting time. Wetting time was recorded with the help of Stopwatch.

Water Absorption ratio

Tablet weight before the placement of Petri dish was noted (W_b) using digital balance. After wetted tablet in

petri dish was reweighting (W_a). Water absorption ratio (R) was calculated according to by below equation.

$$\text{Water absorption ratio(R)}=\frac{Wa-Wb}{Wb}X100$$

Where, W_a = Weight of tablet after water absorption respectively.

W_b= Weight of tablet before water absorption respectively

Disintegration time

This parameter is considered important parameter determination of best formulation. In order to achieve correlation between disintegration time in vitro and vivo, this method is convenience determination disintegration time disintegration time of rapid dissolving tablet of Dapoxetine hydrochloride were determination USP tablet disintegration apparatus with phosphate buffer, pH 6.8 as the medium was 500 ml

and temperature was $37^0C\pm2^0C$. Finally, the time taken for complete disintegration of the tablet.

***In-vitro* dissolution studies**

The *in-vitro* drug release study was performed for all the formulations using USP type II dissolution apparatus under the following conditions. Dissolution test parameters: Dissolution medium 500 ml of phosphate buffer, pH 6.8, Stirring speed: 50 rpm, Temperature: 37 ± 0.5°C, Sampling time 3, 6, 9, 12, and 15 min. At predetermined time intervals, aliquot samples (5 ml) were collected and replenished with the same volume of fresh medium. The aliquot samples (5 ml) were diluted appropriately and the drug content was estimated by using UV - visible spectrophotometer at λ_{max} 230 nm.

RESULTS AND DISCUSSIONS

Drug excipient compatibility [5]

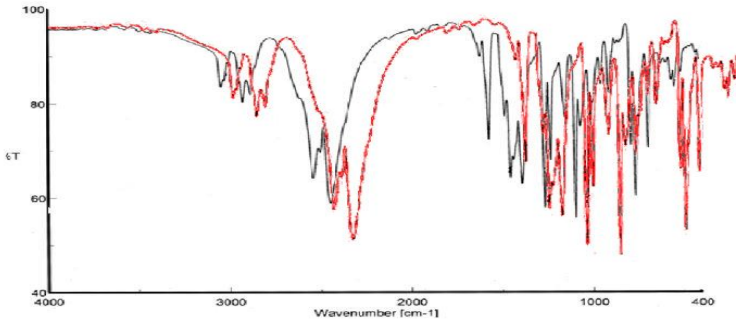


Fig.1 FTIR Spectrum of Dapoxetine hydrochloride and Oro-dispersible Dapoxetine hydrochloride formulation

Table 3 Drug excipient study

Functional Group	Characteristics Peak	Observed Peak			
		Active drug	Oro-dispersible tablet	Dapoxetine	hydrochloride
C-H Stretching	2918-3300 cm^{-1}	3050 cm^{-1}	2910 cm^{-1}		
C=C aromatic	1700-1500 cm^{-1}	1600 cm^{-1}	1550 cm^{-1}		
NO_2	1600-1300 cm^{-1}	1350 cm^{-1}	1300 cm^{-1}		
OH Stretching	3550-3200 cm^{-1}	3340 cm^{-1}	3300 cm^{-1}		
C-Cl	800-600 cm^{-1}	700cm-1	600 cm^{-1}		

FTIR spectrum of Dapoxetine hydrochloride and its Oro-dispersible Dapoxetine hydrochloride tablet formulation was obtained. Dapoxetine hydrochloride was shown frequency at 3050 cm^{-1} due to C-H stretching, 1600 cm^{-1} due to C=C aromatic, 1350 cm^{-1} due to NO_2, 3340 cm^{-1} due to OH stretching, 700 cm^{-1} due to C-Cl. which are match with its Oro-dispersible Dapoxetine hydrochloride formulation at 2910 cm^{-1} due to C-H stretching, 1550 cm^{-1} due to C=C aromatic, 1300 cm^{-1} due to NO_2, 3300 cm^{-1} due to OH stretching, 620 cm^{-1} due to C-Cl. Drug excipients were found compatible after performing FTIR of the Dapoxetine hydrochloride and Oro-dispersible Dapoxetine hydrochloride formulation. It was found that the peaks obtained in formulation were in between the range of main principle peaks and were found to be very near to previously performed FTIR of Dapoxetine hydrochloride. No major deviation in peaks were obtained in FTIR spectra, hence this indicates that drug was compatible with other ingredients.

Evaluation of pre-compression parameters [6,7]

Table 4 Flow properties of powder of solid dispersion and polymers use

Formulation	Angle of Repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's Ratio
F1	25.10±1.20	0.38±1.50	0.46±168	11.50±1.28	1.13±1.42
F2	26.56±1.30	0.39±0.98	0.44±1.25	13.28±1.86	1.14±1.35
F3	25.30±0.90	0.36±1.69	0.43±1.69	12.20±1.43	1.13±1.52
F4	22.28±1.28	0.63±1.80	0.70±1.86	08.60±1.38	1.08±1.46
F5	24.36±1.12	0.43±1.46	0.50±1.58	10.55±1.45	1.12±1.85
F6	25.40±1.42	0.48±1.10	0.55±1.26	09.76±1.53	1.11±1.78
F7	27.10±1.50	0.45±1.14	0.53±1.24	11.58±1.45	1.13±1.76
F8	23.11±1.10	0.42±1.16	0.50±1.33	14.30±1.56	1.14±1.44
F9	26.50±1.05	0.26±1.19	0.23±1.21	13.30±1.88	1.15±1.29

The angle of repose of all formulation was found between 22.28±1.28 to 27.10±1.50 it's indicates excellent flow property. Bulk density was found between 0.26±1.19 to 0.63±1.80 gm/cm^3. Tapped density was found to be 0.23±1.21 to 0.70±1.86 gm/cm^3. Carr's index was found to be 08.60±1.38 to 14.30±1.56% it's indicated excellent flow property of all formulations. Hausner's ratio of all the formulations was found to be 1.08±1.46 to 1.15±1.29 its indicated excellent flow property.

Evaluation of Oro-dispersible Dapoxetine hydrochloride formulation [7,8]

Table 5 Physical properties of Dapoxetine hydrochloride Oro-dispersible tablet

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Wetting time (sec)	Thickness (mm)	Diameter (mm)
F1	3.8±0.82	150±1.36	65±1.10	7±1.25	3±0.98
F2	3.6±1.32	151±1.46	58±1.15	7±1.36	3±1.28
F3	3.9±1.45	150±1.86	42±1.13	7±1.46	3±0.96
F4	4.0±1.52	150±1.56	46±1.04	7±1.52	3±1.68
F5	4.1±0.96	149±1.45	32±1.08	7±1.62	3±1.86
F6	3.9±1.15	151±1.58	24±1.34	7.1±1.72	3±1.68

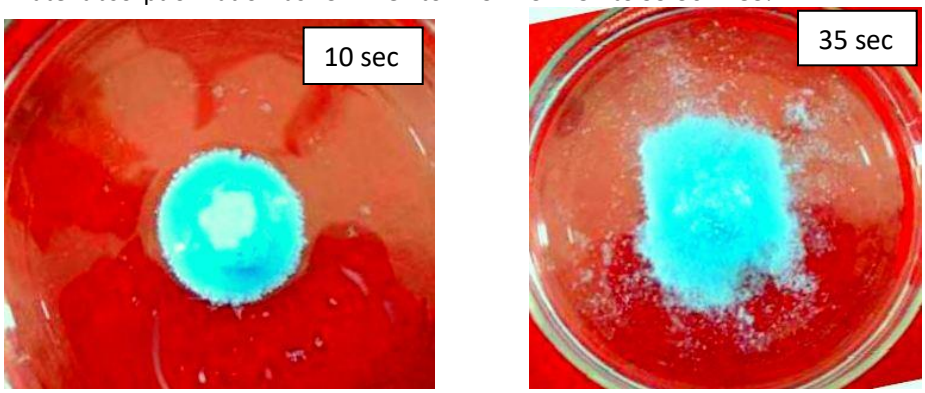
F7	3.5±1.10	150±1.65	50±1.16	7±1.86	3±1.48
F8	3.6±1.16	150±1.69	38±1.06	7±1.56	3±1.63
F9	3.8±1.48	152±1.78	31±1.10	7±1.68	3±1.48

The hardness of all formulation was found 3.5±1.10 to 4.1±0.96kg/cm^2. Weight variation was 149±1.45 to 152.0 ±1.78 mg. Wetting time was obtaining between 24±1.34 to 65±1.10 sec. Thickness was 7±1.25 to 7.1±1.72 mm and diameter was found 3±0.96 to 3±1.86 mm.

Table 6 Physical properties of Dapoxetine hydrochloride Oro-dispersible tablet.

Formulation	Friability (%)	Water absorption ratio (sec)	Disintegration time (sec)	Drug content (%)
F1	0.44±1.27	210±1.26	72±1.88	94.43±1.52
F2	0.40±1.53	118±1.82	68±1.69	95.35±1.36
F3	0.30±1.25	206±1.52	60±1.44	94.23±1.86
F4	0.58±1.46	134±1.82	56±1.80	96.13±1.56
F5	0.76±1.86	150±1.44	40±1.43	97.63±1.86
F6	0.42±1.59	138±1.60	38±1.44	99.36±1.83
F7	0.88±1.68	156±1.80	67±1.67	96.40±1.48
F8	0.38±1.39	155±1.92	62±1.59	94.20±1.26
F9	0.42±1.86	154±1.30	50±1.97	98.82±1.54

The friability of Dapoxetine hydrochloride tablet was found all F1-F9 formulation between 0.30±1.25 to 0.88±1.68 %. Water absorption ratio was 134±1.82 to 210±1.26 sec. Disintegration time was obtained 38±1.44 to 72±1.88 sec. And drug contained was 94.43±1.52 to 99.36±1.83%.



Dapoxetine hydrochloride tablet after 10 sec. Dapoxetine hydrochloride tablet after 35 sec

Fig 2 photos of disintegration time of formulation F-6.

***In-vitro* release studies of Oro-dispersible Dapoxetine hydrochloride formulation**

Table 7 *In-vitro* release studies of Oro-dispersible Dapoxetine hydrochloride formulation

	% Drug Dissolved								
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	34.58±2.25	40.89±2.26	58.56±1.76	38.12±2.89	48.77±2.89	66.74±1.97	45.22±2.76	56.87±2.76	61.44±1.88
6	68.73±1.38	67.52±1.69	70.92±1.39	65.25±1.78	82.77±1.24	87.72±1.23	59.39±1.18	65.30±1.92	81.44±1.38
9	72.62±1.87	83.92±1.65	96.23±1.72	79.27±1.97	91.96±1.45	98.36±1.26	68.61±1.68	77.21±1.88	93.87±1.56
12	77.21±1.75	90.23±1.45	97.46±1.26	85.92±1.49	99.71±1.76	99.25±1.45	79.51±1.23	85.89±1.34	98.99±1.46
15	80.25±1.52	98.56±1.86	99.25±1.72	92.03±1.37	99.72±1.83	99.37±1.35	83.24±1.53	97.24±1.25	99.47±1.78

As concentration of superdisintegrates was increase in Dapoxetine hydrochloride tablet, disintegration and dissolution time was found decreased formulations. F6 contain crospovidone released 98.36±1.26 % drug within nine min. which was fast release formulation among developed other formulation.[9]

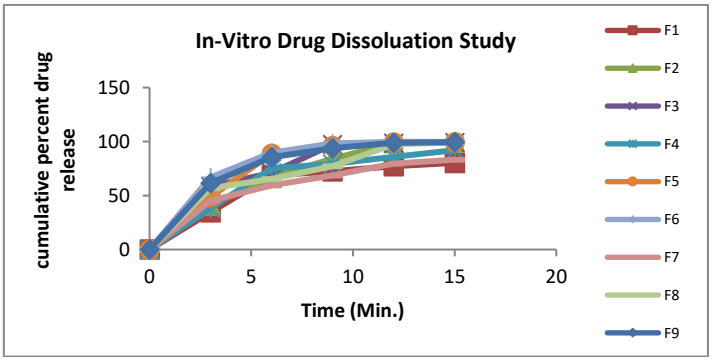


Fig.3 cumulative drug release of all formulation

Pharmacokinetic Drug Release study

Zero order model

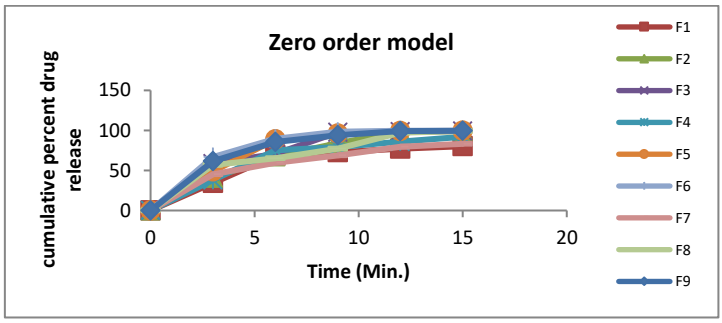


Fig 4 Zero order drug release mechanism of all batches

First order model

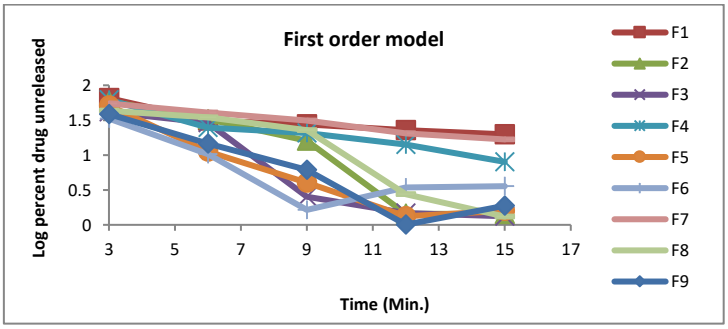


Fig 5 First order drug release mechanism of all batches

Higuchi Model

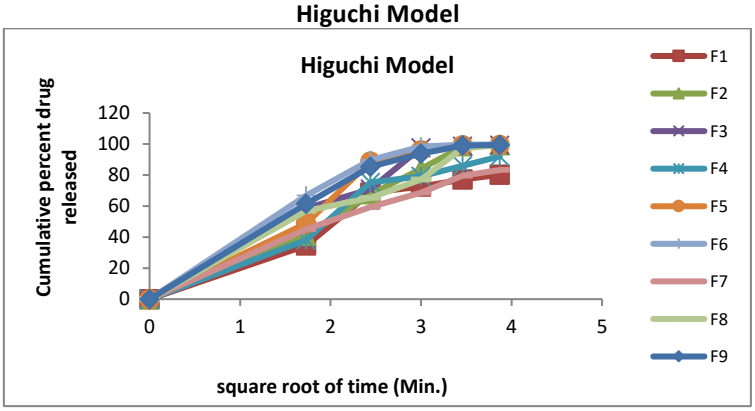


Fig 6 Higuchi drug release mechanism of all batches

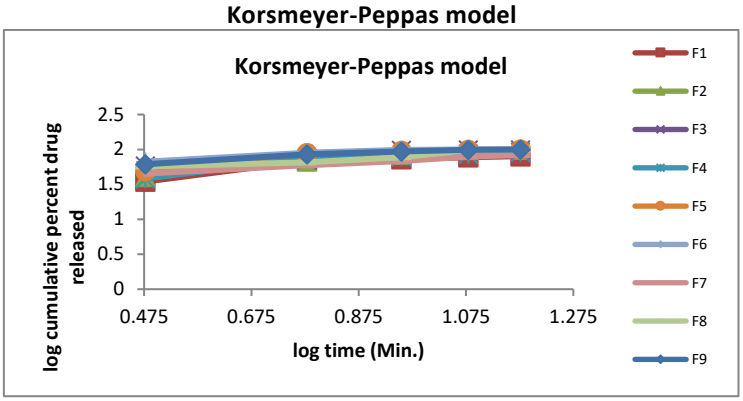


Fig 7 Korsmeyer's and Peppas drug release mechanism of all batches

***In-vitro* Drug dissolution kinetic study**

Table 8 Regression coefficient (R2) different kinetic models of formulation F1 to F9

Formulation Code	Zero-order		First Order		Higuchi Plot		Kormayer - peppas		
Code	R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_p	n
F1	0.9783	1.6323	0.9358	0.0389	0.9684	0.0580	0.9548	1.1489	0.3183
F2	0.9674	1.3840	0.9574	0.0410	0.9853	0.0692	0.9528	1.3978	0.3028
F3	0.9562	1.2896	0.9687	0.0369	0.9715	0.0612	0.9483	1.1983	0.3348
F4	0.9583	1.4086	0.9543	0.0475	0.9654	0.0542	0.9587	1.3146	0.2816
F5	0.9840	1.6528	0.9768	0.0396	0.9728	0.0598	0.9645	1.2973	0.2649
F6	0.9910	1.6873	0.9754	0.0479	0.9968	0.0658	0.9978	1.4873	0.2489
F7	0.9684	1.4090	0.9573	0.0384	0.9548	0.0548	0.9543	1.5216	0.3210
F8	0.9759	1.4958	0.9783	0.0476	0.9658	0.0694	0.9721	1.4287	0.2954
F9	0.9578	1.4085	0.9642	0.0436	0.9873	0.0602	0.9673	1.2943	0.2873

CONCLUSION

Dapoxetine hydrochloride and excipients used in study were found compatible. fast dissolving taste masked Oro-dispersible tablet of Dapoxetine hydrochloride was successfully develop. Among three developed solid dispersion Dapoxetine hydrochloride: Eudragit E-100 (1:1) was possessed no disagreeable taste. Among developed nine formulation of Dapoxetine hydrochloride solid dispersion (1:1), formulation-F6 contain crosspovidone released 98.36±1.26% drug within nine min. which was found as best formulation.

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