International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 4, 2016

Original Article

FORMULATION AND *IN VITRO* EVALUATION OF ORLISTAT ORODISPERSIBLE TABLETS FOR ENHANCEMENT OF DISSOLUTION RATE

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Received: 23 Jan 2016 Revised and Accepted: 18 Feb 2016

ABSTRACT

Objective: The aim of the present study was to formulate the oro dispersible tablets (ODTs) of Orlistat (OST) by direct compression technique using melt granulation method.

Methods: Super disintegrants were used for the preparation of ODTs namely Crospovidone (CP), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG). The powder mixture was subjected to pre compression evaluation like FTIR, Micromeritic, solubility studies and post-compression evaluation like friability, hardness, wetting time, dispersion time, disintegration time and *in vitro* dissolution rate.

Results: FTIR studies confirmed that there was no chemical interaction between the drug and excipients. Micromeritic studies revealed that the powder blend has good flow ability. The results of hardness and friability complied with the official standards. The solid dispersions (SDs) prepared in OST to PEG 6000 ratio of 1:2 were showed good solubility than other SDs and it was selected for formulation development. It was evident from the results that the increase in super disintegrants concentration decreases the wetting, dispersion and disintegration times and CP showed the best results than other super disintegrating agents.

Conclusion: The F4 formulation showed optimum drug release of 98.99 % at the end of 15 min when compared to the other formulations; it might be due to the presence of CP.

Keywords: Direct compression, Melt granulation method, Orlistat, Orodispersible tablets, Polyethylene glycol.

INTRODUCTION

Oral administration is the most popular route. About 50-60 % of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most significantly patient compliance [1, 2]. Solid oral drug delivery systems do not require sterile conditions and are therefore less expensive to fabricate [2-4]. One important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in some patients particularly pediatric [5] and geriatric patients [6]. The problem of swallowing is a common phenomenon in geriatric patients because of fear of choking, hand tremors, dysphasia and in children due to underdeveloped muscular and nervous systems.

Difficulties in swallowing of tablets and capsules also arise whilst water is not available like in diarrhea, coughing during the common cold, allergic conditions and bronchial infections [7]. Oral fast-dissolving drug delivery system (OFDDS) is the one that can increase the patient acceptance by the way of distinctive feature i. e. rapid disintegration and self-administration without water or chewing. Orally disintegrating tablets (ODTs) are solid unit dosage forms like conventional tablets but are composed of super disintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it with water. ODTs are not only indicated for people who have swallowing difficulties but also ideal for active people [8, 9].

Orally disintegrating drug delivery systems can be prepared by the techniques or methods like sublimation [8, 10-13],spray drying [13-16],effervescent method [12, 17-19], lyophilization or freeze drying [13, 20, 21], melt granulation [8, 16, 22, 23], solvent evaporation [5, 24, 25], direct compression [8, 11-13, 26-30], kneading technique [31], molding [8, 13, 16], cotton candy process [13], nanonization [13], crystalline transition process [8], phase transition [8], compaction [8, 16], flat heat process [16], one step dry coated tablet technology [32], suspension spray coating method [33] using super disintegrants and some other co-processed excipients [25].

OST i. e. (S)-(S)-1-((2S,3S)-3-Hexyl-4-oxooxetan-2-yl) tridecan-2-yl) 2-formamido-4-methylpentanoate is drug which has been designed to treat the disease obesity by reversible inhibition of lipases thereby reduces the caloric intake [34, 35] and advised to give adults along with the reduced calorie diet [36]. It also has an effect on reducing the blood pressure and type-2 diabetes [37]. OST comes under the BCS classification class-II drug i. e. low aqueous solubility and high permeability. Formulation additives and characteristics play a vital role on drug dissolution rate and bioavailability of poorly soluble drugs [38]. Based on these considerations, to enhance the bioavailability of OST, it was proposed to formulate the ODTs of OST by direct compression technique using the melt granulation method. Literature also revealed that there was no work reported on the formulation of OST ODTs by melt granulation method. Hence, the attempt was made to formulate the OST ODTs by melt granulation method.

MATERIALS AND METHODS

Materials

OST purchased from RA Chem Pvt. Ltd., Hyderabad, India and PEG 6000, PEG 4000, PEG 1000, CP, CCS, SSG, Talc from S. D. Fine Chem. Ltd, Mumbai, India, Mannitol from Finar Chemical Ltd., Ahmadabad, India, Aspartame, Sodium stearyl fumarate (SSF) from Active pharma labs, Hyderabad, India.

Methods

Preparation of orlistat solid dispersions by melt granulation method

SDs of OST in drug to carrier ratio of 1:1, 1:2, 1:3 were prepared by melt granulation method using PEG 1000, PEG 4000 and PEG 6000 separately. The accurately weighed amount of carrier was melted in china dish in a water bath, and then the calculated amount of OST was added with thorough mixing for at least 1-2 min until to reach homogeneity. Then these melted mixtures were allowed to cool,

followed by drying and the dried product was then made to undergo pulverization by passing through the sieve no.60 and stored in a desiccator for further studies (Table 1). Based on the results from solubility studies, the best composition of drug and carrier was selected for formulation development [6].

Table 1: Composition of OST SDs

Solid dispersions	Drug-carrier ratio
Orlistat**:** PEG 6000	1:1
	1:2
	1:3
Orlistat**:** PEG 4000	1:1
	1:2
	1:3
Orlistat**:** PEG 1000	1:1
	1:2
	1:3

Preparation of OST ODTs

ODTs of OST were prepared by direct compression method by using super disintegrating like CP, CCS, and SSG in different concentrations (Table 2). Based on the solubility studies, the SDs of OST: PEG 6000 in the ratio of 1:2 was optimized for the preparation of ODTs. All the formulations consist of Mannitol, Aspartame, Orange flavor, Talc, SSF and their use as a diluents, sweetener, and flavor, glidant, lubricant respectively. All the excipients of required quantity were blended with OST SDs in a dried mortar for 10 min except SSF and Talc. Prior to compression, SSF and talc were added and mixed gently for 2-3 min. The tablets were punched with BB Tooling in rotary tablet punching machine of 9 mm punch size and the compression force adjusted to give the hardness of official range of 2-4 kg/cm^3 [38].

FTIR studies

The pure OST (drug) and its physical mixture were subjected to IR spectral studies by employing the KBr pellet method using FTIR spectrophotometer (Model-IR Affinity-1, Shimadzu, Japan). One to two milligram of fine solid powder of OST and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of the spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400 cm^{-1} by FTIR spectrophotometer. The spectra obtained for OST, and the physical mixture was compared.

Micromeritic study

The pre compression parameters like bulk and tapped density [39], the angle of repose [40], Hausner's ratio and Carr's index [41] were carried out for powder mixture according to the standard procedures.

Table 2: Formulations of OST ODTs with PEG 6000 (1:2)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug + PEG 6000	180	180	180	180	180	180	180	180	180	180	180	180
CP	5 (2 %)	10 (4 %)	15 (6 %)	20 (8 %)	-	-	-	-	-	-	-	-
CCS	-	-	-	-	5 (2 %)	10 (4 %)	15 (6 %)	20 (8 %)	-	-	-	-
SSG	-	-	-	-	-	-	-	-	5 (2 %)	10 (4 %)	15 (6 %)	20 (8 %)
Mannitol	51	46	41	36	51	46	41	36	51	46	41	36
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Orange flavor	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
SSF	1	1	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	250	250	250	250	250	250	250	250	250	250	250	250

Solubility studies of OST SDs

A known excess amount (12 mg) of OST SDs prepared with PEG 1000, PEG 4000, PEG 6000 in drug to carrier ratio of 1:1, 1:2, 1:3 was transferred individually into an individual boiling tubes containing 10 ml of water to form a saturated solution. Then these solutions were kept for shaking on cyclomixer. After 24 h, the samples were subjected to centrifugation and the supernatant was collected, suitably diluted, estimated for OST concentration using UV-Visible spectrophotometer (Lab India 1700 UV-Visible spectrophotometer) at 215 nm.

Post compression evaluation

Post-compression parameters like friability, hardness, thickness, weight variation, content uniformity, disintegration tests were evaluated for the tablets according to the standard procedures [4, 42].

Wetting time and water absorption ratio (R)

Five circular tissue papers in 10 cm in diameter were placed in a Petri dish containing 10 ml water soluble dye i. e. eosin and this dye solution helps to know the complete wetting of tablet surface. A tablet was carefully placed on the surface of tissue paper in the Petri dish at room temperature. The time required for water to reach the upper surface of the tablet and completely wet them was noted as the wetting time [43]. To check for reproducibility, the measurements were carried out in replicates (n=3). The wetting time was recorded using a stopwatch.

The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where,

W_b and W_a are the weight before and after water absorption respectively.

***In-vitro* dissolution study**

The dissolution test was carried out using Electro lab TDT-06N USP dissolution test apparatus type-II (Paddle method). 900 ml of pH 6.8 phosphate buffers was placed in a vessel and the medium was allowed to equilibrate to the temperature of 37°C ± 0.5°C and set to rotate about 50rpm. The tablet was placed in the vessel and operated for about 30 min. At definite time intervals (2, 4, 6, 8, 10, 15, 20, 25, 30 min), 5 ml of sample was withdrawn, filtered and again 5 ml of fresh buffer was replaced.

Suitable dilutions were done with the buffer solution and analyzed by spectrophotometrically at 215 nm using UV-Visible spectrophotometer (Lab India 1700 UV-Visible spectrophotometer). Each dissolution study was performed for three times, and mean values were taken.

Stability studies

From the obtained results that the formulation F4 was selected for stability studies, and it was performed at 40 ^{o}C/75 % RH for about 3 months. The tablets were analyzed for drug content uniformity and hardness at the end of each month for up to 3 months [44].

RESULTS AND DISCUSSION

FTIR studies

It was performed to know the compatibility between the drug and excipients. The IR spectra of OST physical mixture was demonstrated in Figure 1 and summarized in Table. 3. All the characteristic peaks of OST were presented in IR spectra of its physical mixture indicates that there is no reciprocal action between the drug and excipients.

Micromeritic study

Hausner's ratio was carried out, and it was found to be between 1.20 to 1.23, the results were indicated that the powder blends have good flow properties for compression. Carr's index was ranged from 10.66 to 19.02, indicates that the powder blends have good to fair flow ability for compression. The angle of repose was found to be 29^{0} to 32^{0}, the results were indicated that the powder blends have good flow properties (table 4).

Table 3: Interpretation of IR spectra of optimized formulation (F4)

Functional group	Standard range (cm^{-1})	Orlistat pure drug (cm^{-1})	Orlistat mixture (cm^{-1})
C–H stretching in CH_2	2850-2960	2927	2958
N–H stretching	3500-3300	3300	3309
C=C aromatic stretching	1450-1600	1500	1587

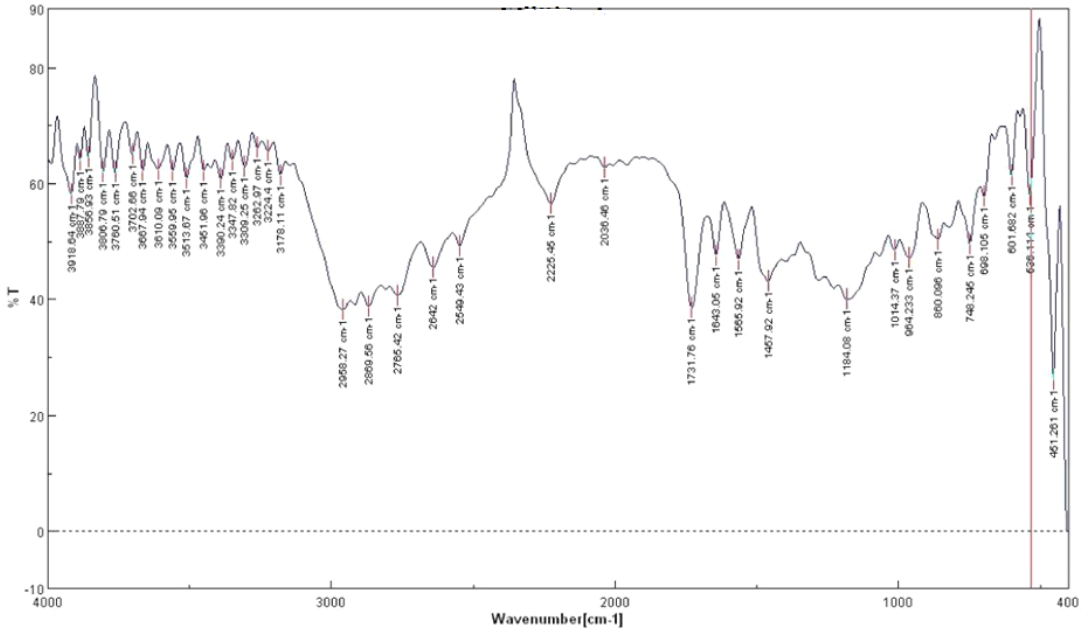

Fig. 1: FTIR spectra of optimized formulation (F4)

Table 4: Pre compression characteristics of OST ODTs

Formulation	Bulk density (gm/ml) Avg ± SD (n=3)	Tapped density (gm/ml) Avg ± SD (n=3)	Hausners ratio Avg ± SD (n=3)	Compressibility index (%) Avg ± SD (n=3)	Angle of repose (θ) Avg ± SD (n=3)
F1	0.435±0.02	0.522±0.15	1.20±0.08	10.66±0.23	32.67±0.21
F2	0.429±0.24	0.518±0.18	1.20±0.21	17.18±0.04	29.08±0.02
F3	0.430±0.08	0.524±0.06	1.21±0.05	17.93±0.32	31.78±0.28
F4	0.432±0.12	0.528±0.19	1.22±0.21	18.18±0.28	30.64±0.85
F5	0.428±0.04	0.518±0.26	1.21±0.09	17.37±0.19	30.36±0.45
F6	0.420±0.18	0.510±0.45	1.21±0.12	17.64±0.32	31.05±0.37
F7	0.416±0.35	0.509±0.08	1.22±0.32	18.27±0.41	32.54±0.41
F8	0.417±0.06	0.515±0.36	1.23±0.38	19.02±0.38	29.67±0.39
F9	0.425±0.23	0.515±0.19	1.21±0.61	17.47±0.52	31.85±0.62
F10	0.421±0.18	0.509±0.65	1.20±0.09	17.28±0.06	29.56±0.09
F11	0.419±0.08	0.515±0.05	1.22±0.28	18.64±0.32	30.17±0.29
F12	0.415±0.38	0.512±0.23	1.23±0.45	18.94±0.24	32.08±0.45

Solubility studies

The solubility of OST SDs prepared with PEG 1000, PEG 4000, PEG 6000 were determined and it was clear from the results that the SDs prepared with PEG 1000 showed the least solubility and PEG 6000 in the ratio of 1:2 showed more solubility in water compared to other grades of PEG, thereby it was selected for formulation development due to its high solubility in water (table 5).

Table 5: Solubility studies of OST and OST SDs prepared with PEG1000, PEG4000, PEG6000

Formulation	Solubility of OST in water (mg/ml)*
Pure drug	0.919±0.53
OST: PEG 1000	
1:1	2.44±0.83
1:2	2.64±0.79
1:3	2.56±0.75
OST: PEG 4000	
1:1	5.87±0.65
1:2	6.21±071
1:3	6.86±0.74
OST: PEG 6000	
1:1	8.58±0.49
1:2	9.72±0.56
1:3	8.90±0.61

*results were expressed in Avg ± SD (n=3)

Post compression studies of OST ODTs

The hardness of all the formulations was ranged from 2.90 to 3.10 kg/cm^2 and it ensures good handling characteristics of all the batches. The percent friability of all the formulations was less than the 1 %, ensuring that the tablets were mechanically stable. All the prepared tablets of OST had been evaluated for weight variation. The weight of all the tablets was found to be uniform and was within the pharmacopoeial limits. The percent drug content of all the tablets was found to be in the range of 98.75 to 99.36 % (which was within the acceptable limits of ±5 %) (table 6).

The results of *in vitro* disintegration time of all the tablets were found to be within the prescribed limits and satisfied the criteria of oral dispersible tablets. Among all the formulations, a formulation with CP (8 %) i. e. F4 showed the lower disintegration time of 27 sec because of among the super disintegrants, the crospovidone have solubility enhancing functionality in addition to the disintegration, dissolution enhancing capability [45, 46-48]. The wetting and dispersion times are most essential for ODTs and those have to be ideally less than 1 min. This rapid disintegration needed to assist in swallowing and enhancing the bioavailability in the buccal cavity [38]. It was clear from the results of wetting time that all the tablets were lies within the prescribed limits and also satisfied the criteria of ODTs and among all the formulations, formulation F4 showed the least wetting time. From the dispersion time studies, the formulation F4 only satisfied the criteria of ODTs i. e. dispersion time <1 min which facilitates the dispersion in the mouth. It was evident from the water absorption ratio studies that all the formulations were absorbed the nearly equal amount of water (table 7).

The decrease in disintegration, wetting and dispersion times might be due to the presence of super disintegrants which absorbs the water thereby swells the tablets and causes rupture of the tablets.

Table 6: Post compression studies of OST ODTs

Formulation	% Weight variation Avg ± SD (n=3)	Drug content (%) Avg ± SD (n=3)	Hardness (kg/cm^2) Avg ± SD (n=3)	Friability (%) Avg ± SD (n=3)	Thickness (mm) Avg ± SD (n=3)
F1	99.9±0.70	98.96±0.47	3.05±0.13	0.48±0.12	2.84±0.032
F2	99.52±0.85	99±0.65	3.10±0.15	0.53±0.08	2.85±0.028
F3	98.9±0.52	99.11±0.52	2.95±0.08	0.44±0.15	2.86±0.024
F4	100.2±1.17	99.15±0.60	2.95±0.10	0.57±0.24	2.86±0.051
F5	99.0±0.49	99.2±0.4	3.08±0.12	0.43±0.85	2.88±0.048
F6	98.8±0.58	98.85±0.58	3.11±0.14	0.56±0.02	2.90±0.052
F7	99.3±0.54	99.31±0.24	2.92±0.08	0.53±0.09	2.92±0.038
F8	100.4±1.0	98.96±0.28	3.0±0.09	0.45±0.54	2.91±0.042
F9	99.6±0.95	99.3±0.38	2.9±0.07	0.6±0.65	2.90±0.040
F10	99.2±0.97	99.36±0.29	3.05±0.08	0.49±0.04	2.89±0.042
F11	99.4±0.86	98.75±0.40	3.05±0.09	0.53±0.23	2.89±0.034
F12	98.5±0.42	99.21±0.38	2.93±0.08	0.58±0.82	2.87±0.031

Table 7: Post compression studies of OST ODTs

Formulation	Wetting time (sec) Avg ± SD (n=3)	*In vitro* dispersion time (sec) Avg ± SD (n=3)	*In vitro* disintegration time (sec) Avg ± SD (n=3)	Water absorption ratio (%) Avg ± SD (n=3)
F1	24.83±0.98	221.33±0.13	116.5±0.37	58.45±0.02
F2	21.16±0.75	180.5±0.24	95.16±0.75	59.25±0.23
F3	14.66±0.51	75.11±0.89	56.50±0.64	58.9±0.09
F4	11.66±0.51	54.10±0.63	27.83±0.16	60.65±0.12
F5	57.33±0.81	244.5±0.09	168.83±0.94	59.88±0.32
F6	22.33±0.36	215.5±0.54	98.12 ±0.63	61.48±0.42
F7	28.11±0.09	177.83±0.16	73.16±0.47	59.55±0.28
F8	19.66±0.81	126.66±0.81	36.66±0.21	60.01±0.62
F9	37.33±0.81	259.83±0.47	171.83±0.16	64.37±0.19
F10	28.33±0.81	225.33±0.81	153±0.89	67.54±0.05
F11	26.66±0.81	186.83±0.75	81.5±0.24	65.50±0.23
F12	36.83±0.16	154.5±0.83	62.66±0.75	65.89±0.41

In-vitro drug releases study

All the formulations of prepared OST ODTs were subjected to *in vitro* release studies using USP dissolution apparatus type-II (paddle method) in pH6.8 phosphate buffer. The results obtained from dissolution study were summarized in Table 8 and presented in Figure 2. In this present study, the dissolution of OST was enhanced by using the super disintegrating agents in different concentrations. Formulations F1-F4, F5-F8 and F9-F12 were prepared by CP, CCS and SSG respectively. Super disintegrants can absorb the water, swells and rupture the tablets, thereby enhances the dissolution and bioavailability [38]. The formulations F1-F4, F5-F8 and F9-F12, showed the cumulative percent drug release (C %DR) ranged from 95 % to 98 %, 85 % to 95 % and 85 % to 92 % respectively in 30 min. Amongst those formulations, F1-F4 formulations made from CP showed highest C % DR and it might be due to its disintegrating, dissolution and solubility enhancing properties but other disintegrating agents mainly have disintegration property only. It was clear from the obtained results, that the concentration of disintegrating agents directly proportional to the dissolution rate. The formulation F4 showed C %DR of 98 % within 15 min. The order of increase in dissolution rate using different disintegrating agents: CP>SSG>CCS.

Table 8: *In-vitro* dissolution data of OST ODT formulations

Time (min)	Cumulative % drug release (mean ± SD, n=3)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
2	27.35±0.28	22.35±0.52	20.46±0.25	28.31±0.23	18.35±0.34	15.43±0.30	22.33±0.25	14.38±0.31	19.33±0.20	23.43±0.16	18.48±0.33	19.4±0.32
4	40.33±0.28	34.36±0.28	29.28±0.19	41.33±0.24	25.5±0.28	23.43±0.32	33.36±0.31	22.1±0.59	28.36±0.32	35.31±0.27	27.18±0.18	27.41±0.26
6	55.46±0.31	45.31±0.27	42.35±0.25	59.33±0.26	37.36±0.25	37.36±0.26	45.46±0.26	36.43±0.30	36.45±0.25	47.36±0.29	34.43±0.23	35.28±0.29
8	69.46±0.27	62.35±0.25	61.31±0.23	73.48±0.34	57.41±0.23	54.38±0.26	62.43±0.23	55.46±0.30	49.43±0.26	53.5±0.34	45.61±0.17	52.43±0.26
10	74.38±0.27	75.48±0.30	76.4±0.36	85.38±0.34	64.55±0.28	67.38±0.37	70.28±0.20	62.46±0.25	55.48±0.26	64.45±0.36	52.41±0.36	65.41±0.33
15	83.35±0.20	87.4±0.31	82.53±0.30	98.6±0.29	72.48±0.35	75.46±0.26	78.41±0.26	75.58±0.27	68.46±0.32	72.6±0.27	61.25±0.55	78.45±0.35
20	94.45±0.30	96.31±0.29	97.31±0.20	98.89±0.32	80.45±0.28	82.31±0.23	86.28±0.24	80.4±0.26	74.58±0.27	78.41±0.14	70.46±0.21	84.51±0.24
25	94.89±0.24	96.57±0.28	97.76±0.28	98.95±0.24	86.5±0.26	87.48±0.24	90.28±0.17	83.48±0.30	78.43±0.27	83.45±0.28	75.41±0.24	88.36±0.18
30	95.78±0.27	96.85±0.32	97.96±0.25	98.99±0.23	89.53±0.19	92.36±0.25	94.46v0.25	95.43±0.19	85.4±0.22	88.45±0.18	90.4±0.33	92.38±0.19

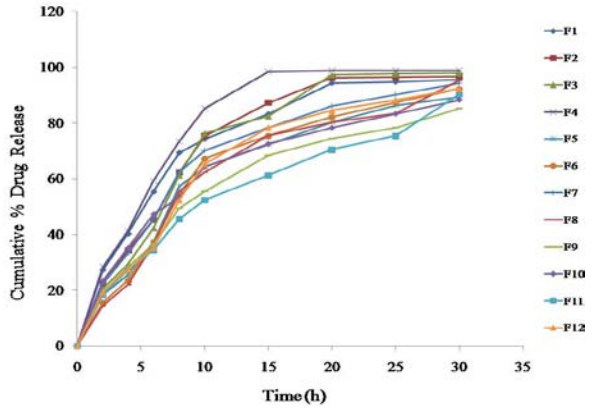

Fig. 2: *In-vitro* drug release profiles of all the formulations

Stability studies

The tablets were analyzed for drug content uniformity, hardness, and this formulation didn't show much variation in any parameter.

It was evident from the obtained results that the formulation F4 was stable and retained its original properties (table 9).

Table 9: Stability studies of formulation F4 stored at 40 ^{0}C / 75 % RH

Formulation code	Tested after time (months)	Hardness (kg/cm^2) Avg ± SD (n=3)	Drug content Avg ± SD (n=3)
F4	1	2.7 ± 0.18	98.54 ± 0.11
	2	2.66 ± 0.23	97.82 ± 0.17
	3	2.65 ± 0.29	97.54 ± 0.22

CONCLUSION

It could be concluded from the results that the SDs prepared with PEG 6000 in the ratio of 1:2 (OST: PEG 6000) showed appreciable solubility in water than other grades of PEG. The formulation F4 contained CP 8 % was found to be the best among all the twelve OST ODT formulations because it had satisfied all the limits of ODTs when compared to the other formulations and it showed 98.99 % drug release at the end of 15 min.

CONFLICTS OF INTERESTS

There are no conflicts of interest

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