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Formulation of taste masked, compression coated, immediate release tablets of oseltamivir phosphate - a preliminary investigation

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ABSTRACT

Oseltamivir phosphate, an antiviral drug, is used for prevention and treatment of influenza. It is the API in 'Tamiflu' which is widely being used against swine flu. It is an ethyl ester prodrug which gets hydrolyzed to the active oseltamivir carboxylate, a viral neuraminidase inhibitor. It is a water soluble, bitter drug. It is available only as a capsule and as oral suspension for reconstitution before use. Immediate release tablets of oseltamivir phosphate have been tried and subsequently compression coated. Initially the drug was evaluated for compression property and excipient compatibility. Core tablet was prepared by direct compression and gave 99.23% release in 20min. A dry compression coating technology using various fillers was employed to achieve taste masking and impart stability. Selected compression coated tablets of oseltamivir phosphate showed 99% release within 45min. In the taste masking study, no bitterness was perceived by the volunteers. The core tablet and compression coated tablets have been evaluated for stability for period of 2 months at 40°C /75%RH which indicated change in the core tablet that affected the dissolution characteristics of compression coated tablet. Dissolution study after one month stability test showed that only one compression coated formula (CC4) containing calcium sulphate dihydrate and lactose monohydrate as coat material has a mean dissolution time of 14.08 and 17.56 min before and after stability respectively with no significant change in the mean dissolution time as indicated by two sided paired t-test at 2 degrees of freedom, 5% level of significance (n=3) where calculated t value 3.1 is less than the table value 4.93. Further study at accelerated conditions revealed gradual discoloration of the core tablet from off-white to cream and then to yellow. Core and compression coated tablets randomly stored for one year between 15-25°C showed no significant change in physical properties of the tablets. Identifying the instability of discolored tablet is scope for further work. CC4 is the immediate release, taste masked tablet of oseltamivir phosphate suitable for excursions of the formulation beyond 25°C. All the compression coated tablets (except CC7) are suitable for taste masking and immediate release among which CC2 and CC9 gave quicker dissolution of the drug.

KEY WORDS: Oseltamivir phosphate, immediate release tablets, compression coating, yellow discoloration, taste masking.

INTRODUCTION

Oseltamivir phosphate (Tamiflu) is used for the treatment and prevention of influenza[1] and is presently being widely used against swine flu. It is an ethyl ester prodrug which gets hydrolyzed by hepatic esterases to the active form oseltamivir carboxylate, a viral neuraminidase inhibitor. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Oseltamivir phosphate is a water soluble, bitter drug with good oral bioavailability. It is advised to be stored below 25°C. It is available as 30mg, 45mg, 75mg capsules and 6mg/ml, 12mg/ml oral suspension for reconstitution before use. Reports on capsule[2], suspensions[3] and taste masking techniques[4,5,6], gastric floating system[7], dry granulation and compaction[8] have been reported. Immediate release tablet dosage form for oseltamivir phosphate is not reported. Tablets are unit solid dosage forms and are widely accepted because of the ease of manufacturing and handling and convenience of self administration. The storage conditions for oseltamivir phosphate indicate that the drug is to be protected from heat, light and humidity. The objective of the present investigation is to formulate oseltamivir phosphate immediate release tablets, achieve taste masking and impart stability by employing compression coating technology.

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MATERIALS AND METHODS

Materials:

Oseltamivir phosphate was a gift sample from Natco Pharma Limited, Hyderabad. Hydrochloric acid, Microcrystalline cellulose, Lactose

Monohydrate, Mannitol, Calcium Sulphate Dihydrate, Magnesium Stearate and Talc were procured from SDFCL. Croscarmellose Sodium and Aerosil were procured from N R Chemicals.

Analytical method[9]:

A UV- spectrophotometric method based on measurement of absorbance at 240nm in 0.1 N HCl media against placebo as blank was used for estimation of oseltamivir phosphate. The method was validated for linearity, accuracy and precision (n=3). A calibration curve was constructed.

Preliminary compression study and evaluation by DSC:

Since there was no tablet formulation reported for oseltamivir phosphate when the present work was undertaken, compressibility study was carried out. Pure drug compact was attempted to be made using the regular tablet compression machine (Rimek .Ltd). The obtained compact has been evaluated for stability of the drug upon subjection to compressive forces, by DSC study. In an aluminum pan, 2-3mg of sample (pure drug/pure drug compact) was placed and crimped with a lid containing a pin hole. The sample was heated at 10°C/min from a temperature range of 100-250°C in a Mettler, Star SW 9.30 model DSC. The thermograms obtained were interpreted.

Drug -Excipient compatibility study:

Physical mixtures of oseltamivir phosphate and excipients were taken in 1:1 ratio in neutral glass vials and maintained at room temperature and at 40°C/75%RH in Humidity chamber (Newtronics) for 4 weeks and analyzed by FTIR. FTIR spectra of pure drug and the physical mixtures were recorded employing Shimadzu FTIR (model – P/N 206-73500-38) by preparing potassium bromide (KBr) disks. The IR spectrum of physical mixtures was observed for the characteristic peaks of oseltamivir phosphate.

Formulation of core tablet:

Core tablets were prepared as per the formula given in Table 1 by direct compression. Aerosil was incorporated based on its stabilizing property against moisture and also as glidant. Drug and excipients (except lubricants) were weighed accurately. They were thoroughly blended in geometrical proportions in a mortar for 15 minutes by ordered mixing. Lubricants were added through sieve 100 on to the powder blend and blended for 5minutes. The resulting blend was compressed to form tablets using 6 mm circular, flat faced punches on Rimek 8 station rotary compression machine. Wet granulation method was avoided to minimize solvent usage and drying process. (Single formulation itself showed adequate properties).

Table 1: Formulation of core tablet

Ingredients(mg/tablet)	OPC
Oseltamivir phosphate equivalent to 75mg oseltamivir	98.53
Micro crystalline cellulose	27.47
Croscarmellose sodium	2.2
Aerosil 200	1.2
Magnesium stearate	3.8
Talc	3.8
Weight of tablet (mg)	137

Determination of precompression parameters:

The tablet blend material and the pure drug were evaluated for angle of repose, bulk density and tapped density.

Angle of repose was determined by fixed funnel method employing 5 gm material.

Angle of repose $\theta = Tan^{-1}(h/r)$ where, r = radius of the pile, h = height of the pile.

Bulk density and tapped density were determined employing Electro lab-USP-ETD-1020 tapped density apparatus. 50ml bulk volume (BV) of pure drug or powder blend was taken and its weight was measured (M). The apparatus was run for 300 taps. The final volume occupied by the material after tapping (TV) was noted. Bulk density = M/BV; Tapped density = M/TV. Compressibility index and Hausner's ratio were calculated as

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped density}} \times 100$$

Hausner's ratio = Tapped density / Bulk density

Evaluation of core tablet:

Assay:

Ten tablets were selected at random and average weight was calculated. Tablets were powdered in a mortar. Quantity equivalent to 98.53mg of oseltamivir phosphate was dissolved in 100 ml of 0.1 N HCl by subjecting to sonication for 5min. The solution was filtered and required dilutions were made and analyzed spectrophotometrically at 240nm for oseltamivir phosphate.

Weight variation:

Twenty tablets were selected at random and weighed individually. The average weight of twenty tablets was calculated. Individual weights of the tablets were compared with the average weight and percent deviation was calculated.

Hardness:
The tablet crushing strength was measured using Monsanto hardness tester (n=5).

Friability:
4gm pre-weighed sample of core tablets were placed in the Friabilator (Electrolab, India) and operated for 100 revolutions. The tablets were dusted and reweighed. The % friability F % $= [(W_0 - W) / W_0] \times 100$, where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test.

Disintegration test:
The disintegration time of the core tablets was determined in 0.1 N HCl maintained at 37±0.5ºC in an ElectroLab, India disintegration test apparatus. The time for disintegration of individual tablets was noted down. (n=6).

***In-vitro* dissolution study of core tablet:**
The *in-vitro* dissolution of core tablet (n=3) was studied in 900 ml of 0.1N HCl maintained at 37±0.5 ºC employing a paddle stirrer operated at 50 rpm in Electrolab TDT 14L dissolution test apparatus for a period of one hour. 5ml samples were withdrawn through filter at predetermined intervals of time and fresh medium was replaced immediately. The samples were suitably diluted and analyzed UVSpectrophotometerically. The data were analyzed by zero order, first order and Hixson Crowell models.

Formulation of compression coated tablets:
Compression coated tablets were formulated using various excipients like mannitol, lactose monohydrate, calcium sulphate dihydrate and, microcrystalline cellulose by direct compression as per formulae given in Table 4. The coat materials were thoroughly blended in a mortar by geometric mixing. The blend was evaluated for precompression parameters as described in the earlier sections. 6mm diameter and 4mm thick core tablet was compression coated. Half the compression coating blend was filled into a 10mm diameter die cavity. The core tablet was placed centrally on the powder bed and remaining half of the compression coating material was added over the core tablet. The material was then compressed using circular concave punches to yield compression coated tablets.

Evaluation of compression coated tablets:
The compression coated tablets were evaluated for drug content, weight variation, hardness, friability, thickness, disintegration time and in vitro dissolution study as described earlier.

Evaluation for taste masking ability:
For psychophysical sensing of the gustatory stimulus, preliminary study to identify taste masking ability was carried out. Two in-house methods were tried on five human volunteers. In one method, simulation of the immersion of tablet in water during swallowing was tried. Initially the volume of water that could be held in the oral cavity was determined and found to be 30ml on an average. The compression coated tablet was then immersed for 15 sec in 30 ml of drinking water taken in a beaker and then removed. That water was sipped and the volunteers were assessed for perception of bitterness. In another method, the tablets were placed on the tongue for 2-5 sec and felt for perception of bitterness. Fresh bitter gourd pulp/juice was used as control. The core tablet and compression coated tablets were evaluated.

Stability study:
Core tablet and compression coated tablets were subjected to preliminary stability study at $40^0C \pm 2^0C$/75%±5%RH for a period of two months in Newtronic 204 ETS humidity chamber. Each tablet was individually wrapped in aluminum foil and packed in polyvinylpyrrolidine bottle for the study. The tablets were analyzed for the appearance, assay and *in-vitro* dissolution. Core and compression coated tablets were also randomly stored for one year between 15-25°C under room conditions and later observed.

RESULTS AND DISCUSSION

Analytical method:
A UV-spectrophotometric method based on measurement of absorbance at 240nm in 0.1 N HCl was used for estimation of oseltamivir phosphate. The method was found to be linear with r^2=0.99 and precise (%C.V < 4%) as given in Table 2. The method obeyed beer's law in the concentration range of 2- 30µg/ml.

Preliminary compression study:
DSC thermogram of pure drug powder as given in Fig. 1, showed an initial flat profile followed by a sharp characteristic endothermic peak with an onset at 203 °C (The observed melting point of the drug was in agreement with the endothermic peak of the thermogram). The thermogram of pure drug compact given in Fig. 2 retains the onset temperature in the endotherm. There is no shift in the endothermic peak of oseltamivir phosphate indicating that there is no physical or chemical change in drug while being compressed to tablet. A hydraulic press would have been a better choice to understand the behavior of the drug during compression but that would be another independent study. Nevertheless the tablet compression machine suits the present need.

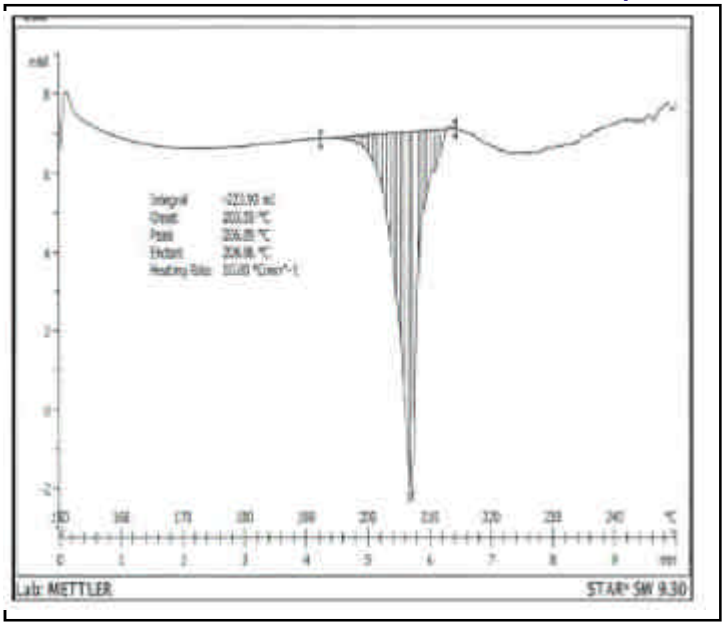

Fig. 1: DSC thermogram of oseltamivir phosphate-pure drug powder

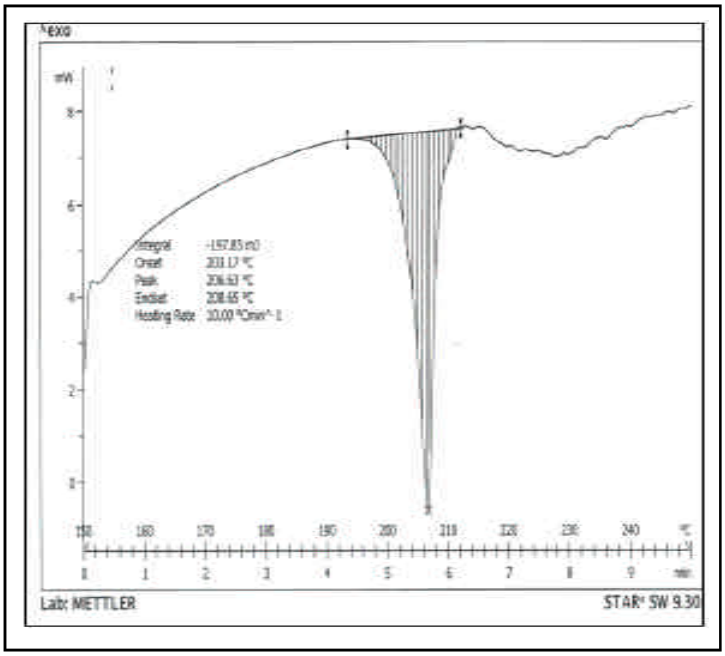

Fig. 2: DSC thermogram of oseltamivir phosphate-pure drug compact

Table 2: Standard curve of oseltamivir phosphate in 0.1NHCl at 240nm

Concentration (µg/ml)	Absorbance (n=3) ($\overline{X}$ ± S.d)	%C.V
2	0.0217 ± 0.0007	3.22
4	0.0354 ± 0.0005	1.41
6	0.0510 ± 0.0017	3.33
8	0.0643 ± 0.0022	3.42
10	0.0745 ± 0.0016	2.22
15	0.1047 ± 0.0004	3.82
20	0.1324 ± 0.0042	3.17
25	0.1704 ± 0.0020	1.17
30	0.2019 ± 0.0082	4.06

Regression equation: $y = 0.0069 x + 0.0081$, $r^2 = 0.99$

Drug-Excipient compatibility study:

Excipient compatibility was evaluated using FTIR spectrum studies. IR spectrum of pure drug suggests the presence of ester bond at 1720cm^{-1}, amine group at 3354cm^{-1}, amide at 1662 cm^{-1} that are present in oseltamivir phosphate. As per the study method, the IR spectra of various drug and excipient mixtures retained the characteristic peaks of drug indicating no chemical interactions. On physical observation, mild color change from off white to pale cream color in mixture of drug with mannitol and with magnesium stearate was observed, which has to be further evaluated

Formulation and evaluation of core tablet:

Pure drug was crystalline in nature having an angular shape (on optical microscopic observation). Poor flow as indicated by high angle of repose may be attributed to the shape of the drug particles. Bulk and tapped densities were found to be 0.45 gm/ml and 0.51 gm/ml respectively as given in Table 3. Hausner's ratio and Carr's index reveal the same. For the core blend where glidant and lubricant were incorporated randomly at 3 %, the flow improved and angle of repose was 15.774±1.08. Hausner's ratio was found to be 1.17. Carr's index was 14.54 % indicating that the powder blend had good compressibility.

The evaluation characteristics of the core tablet (Table 3) are within the IP specifications for immediate release tablets. *In vitro* dissolution study of immediate release core tablet showed 99.23% dissolu-

Table 3 Core tablet properties

Pre-compression parameters			Core tablet evaluation		Dissolution kinetics		
	Pure drug	OPC			Order	R^2	Rate constant
Angle of repose (n=6)	35.32	15.7±1.08	%Weight variation (n=20)	1.06			
Bulk density (gm/cm^3) (n=3)	0.4	0.65±0.02	Hardness (Kg/cm^2)(n=5)	2.5	Zero order	0.928	4.43 mg/hr
Tapped density (gm/cm^3) (n=3)	0.5	0.77±0.003	% Friability(4g)	0.107			
Hausner's ratio	1.25	1.17	Disintegration time (min)(n=6)	5	First order	0.964	0.18 min^{-1}
Carr's index	20	14.54	% Assay (n=10)	99.14±0.12	Hixson- Crowell	0.976	0.18 mg $^{1/3}$ min^{-1}

tion in 20 minutes. Water soluble materials, direct compression method of tablet preparation, fast wicking rate of microcrystalline cellulose and use of croscarmellose sodium resulted in rapid disintegration and quick dissolution. R^2 value is slightly higher for first order (0.96) than zero order (0.92). Thus dissolution from OPC follows first order kinetics and Hixson Crowell mechanism.

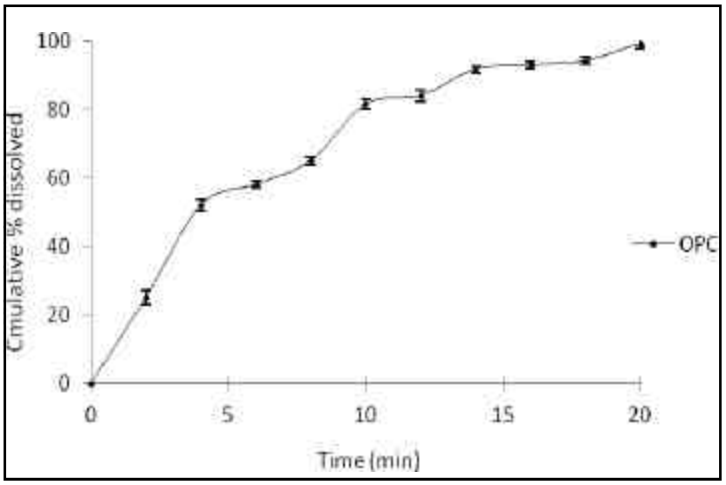

Fig.3: Cumulative % dissolved vs. time plot of OPC tablet

Table 4: Formulation of compression coated tablets

Ingredients (mg/tablet)	CC1	CC2	CC3	CC4	CC5	CC6	CC7	CC8	CC9
OPC	137	137	137	137	137	137	137	137	137
Mannitol	210	210	210	-	-	-	105	105	105
Lactose monohydrate	-	-	-	210	210	210	105	105	105
Calcium sulphate dihydrate	80	-	40	80	-	40	80	-	40
Microcrystalline cellulose	-	80	40	-	80	40	-	80	40
Croscarmellose sodium	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total weight	445	445	445	445	445	445	445	445	445

Precompression properties of coat material:

All formulation blends given in Table 4, were studied for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and data is given in Table 5. Angles of repose were in the range of 15.506± 0.98 to 28.35±0.90 showing that the blend of powder was free flowing. Carr's index was in between 11.89 to 22.294 indicating that all batches of powder blends were having good compressibility. Hausner's ratio was found to be within the limits 1.14 to 1.28. The results showed that all the formulations showed good flow properties.

Table 5: Precompression parameters of compression coating blends

Formula Code	Angle of repose (n=6) Mean ±SD	Bulk density (gm/cm³) (n=3) Mean ±SD	Tapped density (gm/cm³) (n=3) Mean ±SD	Hausner's ratio	Compressibility index
CC1	15.50±0.98	0.59±0.006	0.69±0.008	1.166	16.666
CC2	24.2±0.1.08	0.48±0.005	0.61±0.004	1.2858	22.294
CC3	24.67±0.92	0.40±0.012	0.72±0.014	1.126	14.53
CC4	25.97±0.82	0.59±0.004	0.74±0.003	1.134	11.89
CC5	23.6±0.72	0.51±0.005	0.69±0.003	1.3598	26.462
CC6	28.35±0.90	0.89±0.024	0.74±0.002	1.150	13.24
CC7	17.04±0.80	0.508±0.02	0.59±0.02	1.164	21.4.35
CC8	20.83±0.53	0.61±0.04	0.72±0.003	1.140	14.53
CC9	27.78±1.03	0.550±0.014	0.66±0.004	1.212	17.503

Preparation and evaluation of compression coated tablets:

Compression coated tablets were prepared by direct compression. The tablet characteristics are given in Table 6. Weight variation was in the range of 0.67-1.4% (permitted deviation- 7.5%), hardness ranged from 3.4 - 4.2 Kg/cm², thickness was between 3.9 mm to 4.2mm, friability ranged from 0.1 to 0.12% and assay was 97.71±0.01 % to 99.08%. This indicates that the evaluation parameters for all the formulations are within the limits. In disintegration test initially outer coat disintegrated in 2-3min followed by core tablet disintegration within 5min. Disintegration time ranged from 6-12 min (< 15min).

Table 6: Characteristics of compression coated tablets

Formula code	Assay (n=5) Mean ±SD	%Weight variation (n=20)	Hardness# of core tablet (Kg/cm²) (n=5) Mean	Thickness (mm) (n=5) Mean	Friability (%) (6 gm)	Disintegration time (min) (n=6) Mean
CC1	98.43±0.007	0.67	2.2	5.1±0.04	0.105	12.33
CC2	98.15±0.31	1.1	2.3	5.12±0.03	0.107	7.4
CC3	98.75±0.91	0.88	2.5	4.9±0.05	0.114	8.33
CC4	97.71±0.008	0.98	2.3	5.1±0.06	0.12	8
CC5	98.54±0.15	1.2	2.2	5.1 ±0.03	0.15	6.25
CC6	98.15±0.31	1.3	2.2	5.0±0.02	0.1	6
CC7	99.08±0.28	1.2	2.25	5.1±0.01	0.11	10
CC8	98.53±0.001	0.98	2.8	5.0±0.02	0.11	6.66
CC9	98.07±0.02	1.4	2.2	5.0±0.03	0.1±0.15	5.83

 # On hardness test, the compression coating initially ruptured followed by core tablet breakage. The hardness of coat was between 1.5-2kg/cm².

***In vitro* dissolution study of compression coated tablets:**

Invitro dissolution study of immediate release compression coated tablets was conducted in 0.1 N HCl. According to I.P specification, complete release of oseltamivir phosphate is to be achieved within 45min. Fig. 4 shows that within 45 minutes the cumulative % dissolved from the compression coated formulations was found to be

between 98.47 - 101.51 % (except for CC7 where only 83% dissolved) indicating that immediate release profile could be achieved by compression coating technology. From the correlation coefficient values given in Table 7 it may be observed that 'r' values for zero order and first order are close to each other with zero order r value being slightly higher than r values of first order kinetics. Zero order kinetics may not impact the *in vitro* dissolution rate because the drug from the tablet is completely dissolved within 45 minutes. 'r' value for Hixson Crowell model kinetics too is above 0.9 for most of the formulae. $t_{90\%}$ was best for CC1, CC2, CC8 and CC9 being 18min, 15min, 17min, 16min respectively, which is in agreement with $\%D.E_{20}$ being 44.51, 52.16, 54.38, 78.03 respectively. All the compression coated formulae fit the release specifications for immediate release tablets.

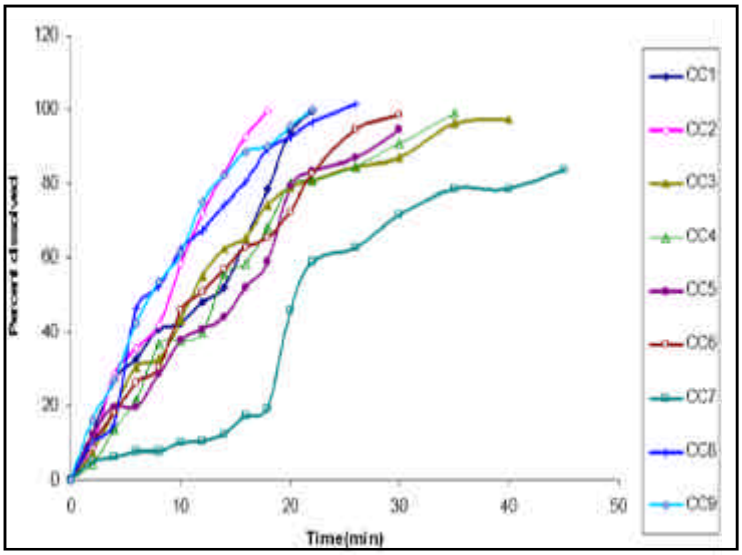

Fig. 4: Cumulative % dissolved vs. time plot of Compression coated tablets

Table 7: Dissolution Characteristics of Compression coated tablets

Code	Correlation coefficient 'r' value			Dissolution parameters (n=3)				
	Zero order	First order	Hixson crowell	$t_{90\%}$ (min)	$\%D.E_{20}$	K_0 (mgmin^{-1})	K_1 (min^{-1})	K_{hc} (mg$^{1/3}$min^{-1})
CC1	0.992	0.860	0.910	18	44.515	4.1393	0.1361	0.1401
CC2	0.994	0.858	0.881	15	52.165*	5.348	0.2256	0.244
CC3	0.970	0.983	0.993	31	42.923	2.5086	0.0891	0.0897
CC4	0.987	0.928	0.928	30	37.517	3.0395	0.1073	0.1233
CC5	0.994	0.938	0.962	27	35.298	5.348	0.2256	0.244
CC6	0.995	0.914	0.951	24	40.239	3.3691	0.1181	0.1232
CC7	0.975	0.957	0.957	45#	11.806	2.221	0.0451	0.0552
CC8	0.966	0.960	0.935	17	54.386	3.4978	0.1644	0.1799
CC9	0.964	0.892	0.949	16	78.0376	3.4110	0.2238	0.1931

$*D.E_{18}$ # $t_{80\%}$

Evaluation for taste masking ability:

Preliminary taste masking study by the two in house methods indicated that bitterness was perceived by the volunteers for the bitter gourd pulp juice and core tablet but not for the compression coated tablets. The objective of masking the bitter taste of oseltamivir phosphate could be fulfilled by compression coating technology. The taste masking study may be further refined employing qualified tasters as volunteers.

Stability study:

The data for preliminary stability study of oseltamivir phosphate core tablet and compression coated tablets under accelerated conditions of 40±2^{0}C/75±5%RH for one month are given in Table 8. The core tablet had no significant change in assay but its color changed from off white to cream, hardness increased slightly from 2.5 to 2.7 Kg/cm^2, disintegration time increased from 5min to 10min. I*n vitro* dissolution study of core tablet showed that the dissolution prolonged (Fig. 5) and t_{90}% increased from 20min to 60min. All the compression coated formulations did not show any change in appearance and drug content. Hardness, disintegration time and dissolution profile varied (Fig. 6,7 and 8) on exposure to stability testing conditions. For all the compression coated tablets on visual observation, the outer coat dissolved or dispersed within 2-3 min but the disintegration of core tablet took longer time.

Table 8: Stability study data of core and compression coated tablets

Parameter	Core tablet	
	Initial	After accelerated study
Color	Off white/ dull white	Cream (1.5 months) Yellow (beyond 2.5 months)
Hardness (kg/cm^2)	2.5	2.7
Disintegration time(min)	5	10
Assay (n=5)	99.14 ± 0.12	98.16 ± 0.81 (1 month)
$t_{90\%}$ (min)	20	60
% friability	0.11	0.12

Parameter	Compression coated tablets(CC1-CC9)	
	Initial	After study
Color	White	white
Hardness (kg/cm^2)	Coat alone :1.5-2.0	Coat alone: 1.2
Disintegration time(min)	After stability study, the compression coating disintegrated within 2-3 min but the core tablet took longer time to disintegrate	
Assay (n=5)	97.71 - 99.08	97.43 - 99.54
$t_{90\%}$ (min)	Ranged from 15 min (CC2) to 30min (CC4) and extended beyond 45 min(CC7)	Ranged from 28 min (CC8) and prolonged beyond 60 min (CC9)
% friability	0.11	0.25

The increased disintegration time and prolonging of drug dissolution maybe due to the effect of moisture on the microcrystalline cellulose present in the core tablet. Microcrystalline cellulose is reported to

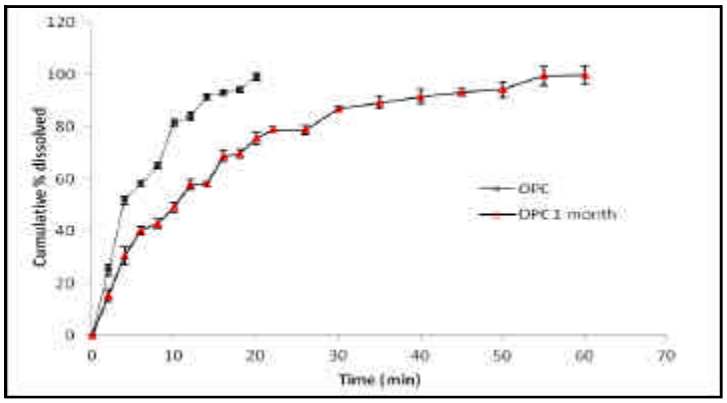

Fig. 5 Dissolution profile of core tablet before and after stability test

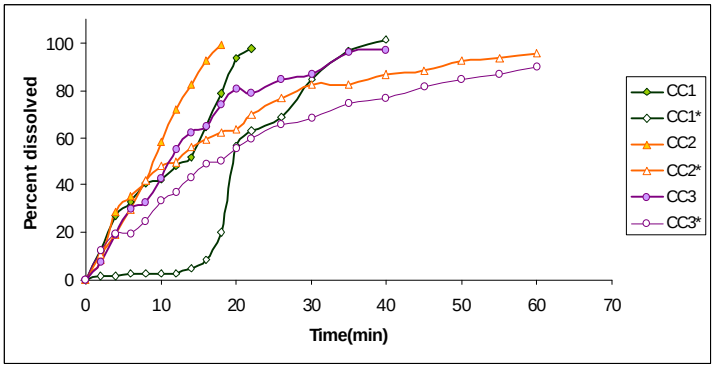

Fig. 6 Dissolution profile of CC1, CC2 and CC3 before and after stability study*

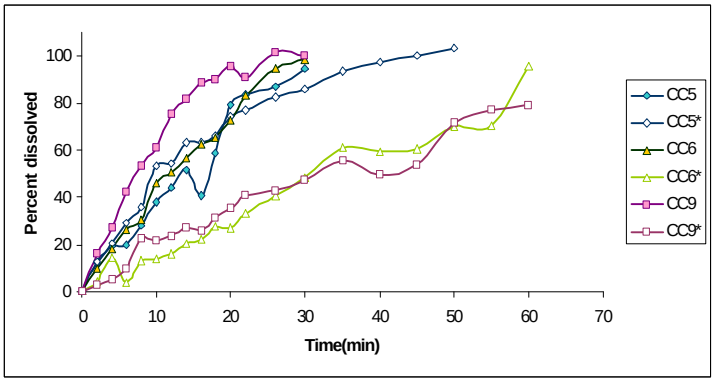

Fig. 7 Dissolution profile of CC5, CC6 and CC9 before and after stability study*

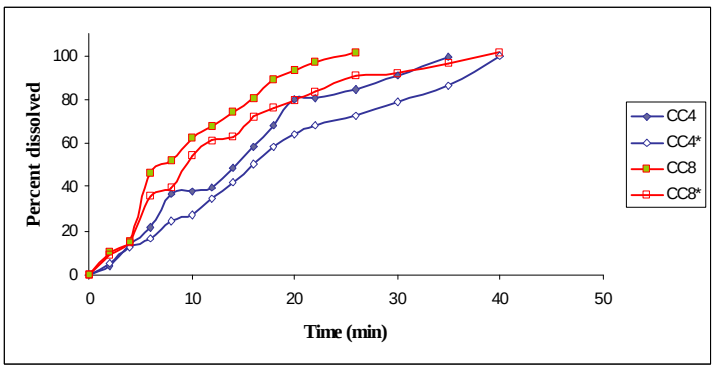

Fig. 8 Dissolution profile of CC4 and CC8 before and after stability study*

undergo physical change, particle size enhancement and forms strong pendular bonds on the surfaces due to uptake of excess of moisture[10, 11] when the tablet was exposed to 40°C /75% RH. Additionally, since in direct compression method the lubricating agents will coat the individual particles, the effect of lubricants on disintegration and dissolution need to be studied. Thus the disintegration time and subsequently drug dissolution time may have increased. Physico-chemical changes occurring in the drug have not been undertaken in this study. Only formulation CC4 showed almost similar disintegration time and dissolution profile before and after one month stability test. $t_{90\%}$ value for CC4 was 32 and 35min, mean dissolution time was 14.08 and 17.56min respectively before and after stability. When the MDT was evaluated by two sided paired t-test at 5% level of significance and 2 degrees of freedom(n=3), the calculated value t =3.1 is less than table value of 4.93. There is no significant difference in mean dissolution time of CC4. Since calcium sulphate is moisture resistant coating[1] moisture did not reach core, so the effect of moisture on microcrystalline cellulose and it subsequent adverse effect on dissolution could be avoided.(dissolution study of CC7 was not conducted after stability test).

Further study of the oseltamivir phosphate tablets at accelerated conditions revealed gradual discoloration of the core tablet from off - white to cream and then to yellow (Fig. 9). A shift in the DSC thermogram of the core tablet indicates instability (Fig.10). Drug-excipient compatibility study based on the mini formulation or n-1 design may have yielded some more information than binary physical mixture method. Core tablets and the compression coated tablets stored randomly for one year between 15-25°C showed no change in physical appearance as given in Fig. 11. There was no significant change in the tablet hardness, friability and disintegration time (*in vitro* dissolution was not performed).

Fig. 9 Yellow discolored core tablet concealed by compression coating

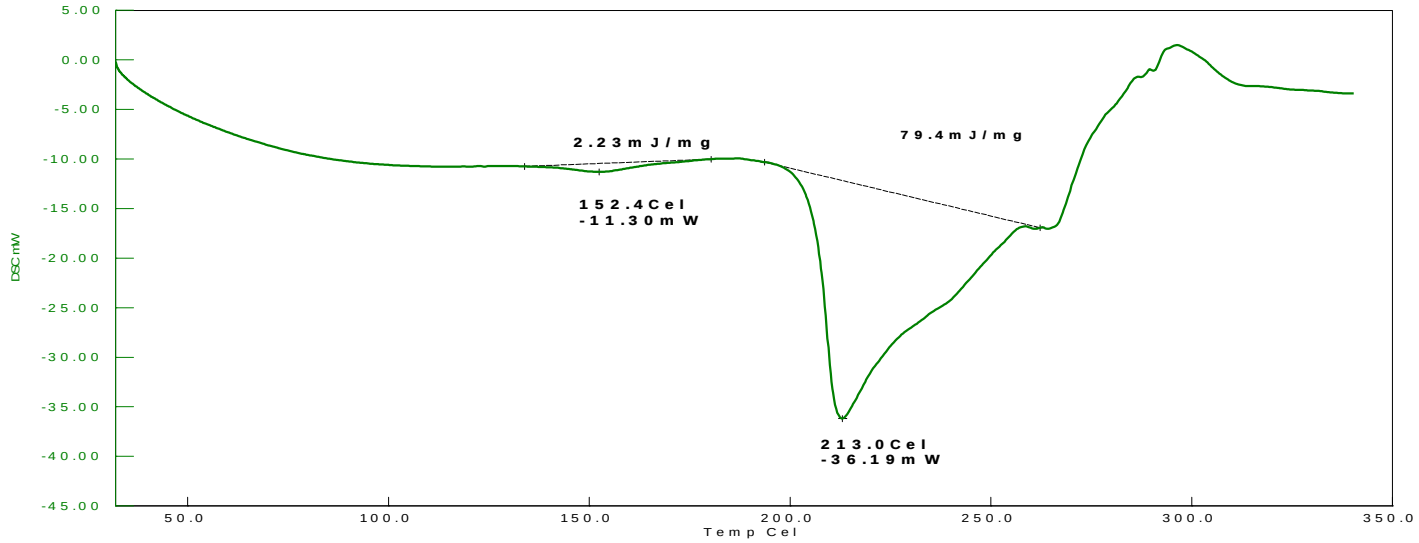

Fig. 10 DSC thermogram of core tablet after accelerated stability study

Fig. 11 Oseltamivir Phosphate Tablets after one year storage between 15-25°C From left - core tablets, compression coated tablets and core revealed tablets

CONCLUSIONS:

Based on dissolution and preliminary stability data CC4 can be considered a suitable immediate release, taste masked, tablet formulation of oseltamivir phosphate which would permit excursions of the formulation beyond 25°C. If packaged and stored properly all the compression coated tablets (except CC7 due to slower dissolution) are suitable for immediate release among which CC2 and CC9 gave quicker dissolution of the drug. Thus taste masked compression coated immediate release tablets of oseltamivir phosphate could be formulated. Identifying the instability of discolored tablet and solid state stability studies of osletamivir phosphate in the tablet dosage form employing valid stability indicating methods is scope for further work. To prevent the discoloration, the core tablet/compression coating may be formulated with specific compatible and stabilizing excipients.

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