Formulation and *In-vitro* Evaluation of Sublingual Tablets of Ondansetron Hydrochloride using Coprocessed Excipients

Ajeet M. Godbole, Sandesh N. Somnache*, Shalin P. Thakker, Sudhir R Iliger, Ashwini S. Joshi, Bhautik V. Patel

SET'S College of Pharmacy, S.R. Nagar, Dharwad-580002, INDIA

ABSTRACT

The formulation of sublingual tablets of Ondansetron HCl was carried out by using direct compression technique and evaluation tests were carried out as per pharmacopoeial specifications. Poor compressibility problem of Mannitol was overcome by coprocessing it with maltose and corn starch in varying ratios. The results of evaluation tests indicate that the ratio of Mannitol: Maltose: Corn starch: 19:2:1 gave better tableting performance with respect to precompression & postcompression parameters. It was also observed that increase in maltose content, increased the hardness but negatively affects disintegration and drug release and vice versa. Furthermore the study on effect of superdisintgrants shows that Crospovidone gives faster disintegration and satisfactory drug release in concentration of 4% compared to that of Sodium starch glycolate & Croscarmelose sodium. Formulation using a bioadhesive polymer PVP K 30 in ratio of 0.5% showed uniform release of drug over a period of 20 minutes with complete solubilization of tablet compared to that of gelatin and carbopol 934. On numerical optimization of prepared formulations, three formulations were suggested by Design Expert 8.0.7.1(Trial Version), among that Formulation B gave better correlation between predicted value and observed value. Thus Formulation B was chosen as global best formulation.

Key words: Sublingual Tablet, Direct Compression, Co-processing of excipients, Historical Data Optimization, Ondansetron HCl.

INTRODUCTION

Vomiting is the reflex action of ejecting contents of stomach through the mouth and sometimes through the nose, while nausea is the feeling that one is about to vomit. The act of emesis and sensation of nausea occurs due to a variety of reasons like ingestion of drugs, gastric irritant, chemotherapy, radiotherapy GI infections.[1] Vomiting occurs due to stimulation of the emetic center (Chemoreceptor Trigger Zone) at medulla oblongata. Nausea is accompanied by reduced gastric tone.[2]

Ondansetron is a highly selective 5-HT_3 receptor antagonist and numerous studies have demonstrated its superior antiemetic efficacy in prevention of nausea and vomiting. Until, now only intravenous and oral formulations of 5HT_3 receptor antagonists were available. Recently a new formulation of a 5HT_3 receptor antagonists in the form of suppositories, nasal drug delivery formulations, transdermal drug delivery systems have been developed.[3,4] The intravenous formulation is suitable for in-patient, but it is not ideal in ambulatory conditions. The oral dosage form is not appropriate for all patients, in particular for individuals with difficulty in swallowing or those with poorly controlled nausea or vomiting.[5] Transdermal or nasal formulations though have number of advantages over oral or parenteral route, difficulties in formulation & high cost of manufacturing make it nonviable. To over-

Submission Date : 17-04-13
Revision Date : 22-09-14
Accepted Date : 06-11-14

DOI: 10.5530/ijper.48.4s.2

Correspondence Address
Prof Sandesh N. Somnache
Department of Pharmaceutics, SET'S College of Pharmacy, S.R. Nagar, Dharwad-580002, INDIA.
Email: sandeshsomnache@gmail.com

www.ijper.org

come these problems oral mucosa can be used as an alternative route for administration of antiemetic drugs.

Drug absorption through a oral mucosa is generally efficient due to absence of the stratum corneum epidermis. Mucosal surfaces are rich in blood supply, providing the means for rapid drug transport directly into the systemic circulation. Oral transmucosal administration also bypasses the enterohepatic circulation and prevents immediate destruction of therapeutic agent by gastric acid or first-pass effects of hepatic metabolism.[6] Oromucosal drug delivery can be categorized into sublingual, buccal, palletal and gingival. The sublingual mucosa is more permeable & show faster onset of action compared to other oromucosal routes.[7]

Sublingual route refers to a method of administering therapeutic substances through the floor of mouth in such a way that the substances are rapidly absorbed through the rich vasculature that exists under the tongue rather than through the digestive tract, which allows the drug substances a more direct contact with the blood circulation, thus providing fast onset of action.[8] Although various sublingual formulations are available, tablet formulation is the most preferred dosage form.[9] Sublingual tablets containing soluble ingredients get dissolved in a specified time without causing any discomfort.

Direct compression is simplest method of tablet manufacture as it required less equipments, has minimum processing steps, reduced labor cost. It is a dry process hence deterioration of active ingredient has been prevented. Further advantage of direct compression is that tablets disintegrate into their primary particles rather than granular aggregates. The resultant increase in surface area available for dissolution results in faster drug release.[10] The direct-compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential. Difficulty in getting suitable excipients with high functionality creates opportunities for the formulation scientists to develop newer grades of existing excipients. Developing newer grades of existing excipients with varying physicochemical properties has been carried out by using techniques referred as "Coprocessing" or "Particle Engineering" of excipients. Co-processing is a novel phenomenon of developing a new single-bodied excipient by interacting two or more excipients at sub-particle level with an objective to provide a synergy of functionality improvement as well as masking of the undesirable properties of individual excipients. A combination of plastic & brittle materials is necessary in order to have an optimum tableting performance.[11]

MATERIALS AND METHODS

Ondansetron Hydrochloride supplied as a gift sample by Samartha Lifesciences Pvt Ltd. Mannitol, Maltose, Corn Starch, PVP K30, Carbopol 394 and Gelatin were purchesed from Himedia labs, Mumbai. Super-disintegrants (Crospovidone, Croscarmelose sodium and Sodium starch glycolate) were purchased from Yarrow chemicals, Mumbai.

Selection of Excipients for Coprocessing:

Mannitol is mostly used as a diluent for the direct compression. But it is a poorly compressible saccharide with high hygroscopic nature. This may cause difficulties in tableting performance leading to poor mechanical strength, andunsatisfactory flow characteristics. According to scientific literatures, combination of poorly compressible saccharides and highly compressible saccharides gives a good mechanical strength. Maltose is high compressible saccharide usually used in the preparation of chewable tablets. Combining mannitol & maltose gives better hardness to the formulation. Flowability, compressibility of a formulation could be improved by Coprocessing of a brittle material with a fibrous material. Starch is the most widely used filler/binder in tablet formulations, generally it is used in a concentration of 5-25% w/w as binder & 3-15% w/w as tablet disintegrant. Thus in the present work Mannitol was co-processed with maltose & corn starch and used as diluent for the preparation of sublingual tablets of Ondansetron HCl.[12-14]

Coprocessing of mannitol

Physical mixtures of mannitol and corn starch were prepared in different ratios as mentioned in the (Table 1). Maltose was dissolved in specified quantity of distilled water. The prepared maltose solution was added to mannitol-corn starch mixture with constant stirring at 200 rpm using magnetic stirrer. Stirring was continued up to 30 minutes. The resultant mixture was kept in a refrigerator overnight & then dried at 70^0 C. The dried mass obtained was ground & passed through sieve No. 44 to obtain fine granules.

Table 1: Ratios of excipients for Coprocessing

	Mannitol (gm)	Maltose(gm)	Corn Starch(gm)	Distilled Water (ml)
CP mannitol I	20	1	1	10
CP mannitol II	19	2	1	10
CP mannitol III	18	3	1	10

Formulation of sublingual tablets of Ondansetron HCl:

Accurate amount of the Ondansetron HCl and all additives were homogeneously blended in geometric dilutions. Magnesium stearate & Talc ware added to the mixture. Tablets were directly compressed by a 10 station Rotary Tablet Press (Cadmac) with 7.5 mm concave punch and die set. A compression force of 4 kg/cm^2 and a weight of 125 mg were maintained for all the tablets. Compositions of each formulation are given in (Table 2.)

Evaluation of tablets for Precompression parameters:

Angle of Repose[15]

Angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the equation $\theta = Tan^{-1} h/r$.

Density of powder[16]

A powder blend from each formulation was introduced in to a 10 ml glass measuring cylinder. The initial volume and weight was noted. The cylinder was tapped 50 times on to a hard surface from a height of 2.5 cm at an interval of one second. Tapped volume was noted. Based upon the data obtained Untapped Bulk Density and Tapped Bulk Density were calculated.

Compressibility Index and Hausner's Ratio[16]

Compressibility Index and Hausner Ratio of powder blend was determined by using Tapped bulk density and untapped bulk density.

Evaluation of tablets for Post compression studies:

Hardness [17]

A diametric compression test was performed according to European Pharmacopoeial method 2.9.8 using Monsanto Hardness Tester. According to standard literature in case of sublingual tablet hardness of 2 kg/cm^2 was acceptable.[18]

Friability[19]

The friability test was performed according to the IP guidelines. Since the tablet weight (125 mg) was always less than 650 mg, a random sample of whole tablets corresponding to 6.5 g was dedusted, accurately weighed, and placed in the drum of a Roche Friability tester (Mfg by Koshiash Industries). Drum was rotated 100 times and tablets were removed, dedusted, and accurately weighed. A maximum weight loss of not more than 1.0% was considered acceptable.

Uniformity of weight [19]

As per IP guidelines to perform test for uniformity of weight 20 tablets from each batch were selected randomly and their average weights were calculated using a digital weighing balance (Essae Teraoka ltd). Percentage weight difference was calculated and checked with IP specifications.

Wetting time[20]

The test for wetting time was carried out by using two layers of a rectangular absorbent paper (11 cm x 7.5 cm) fitted into a Petri dish & wetted thoroughly with distilled water. The tablet was placed at the center of the plastic dish and the time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was recorded using a stopwatch.

Determination of drug content[21, 22]

Twenty tablets from each formulation were weighed and powdered. 10 mg of the powder was weighed accurately and dissolved in 100 ml of distilled water. The mixture was sonicated (Equitron) for 180 seconds and filtered through Whatman filter paper No. 40. The filtrate was further diluted with distilled water and absorbance was measured at 310 nm. By using slope of standard calibration curve the amount of Ondansetron HCl was calculated.

Disintegration Test[15]

Disintegration test was carried out according to USP NF standard. One tablet was placed in each of the six tubes and the using distilled water maintained at 37^0 C ± 2^0 C and the tablets were observed for disintegration. At the end of the time limit i.e. 2 minute as directed for sublingual tablet, the basket from the fluid was lifted up and observed for the tablets complete disintegration.

In-vitro drug release profile[23]

In vitro drug release studies were carried out by adopting Modified European Pharmacopoeial method by using distilled water as dissolution medium at 37^0 C ± 0.5^0 C with at 50 rpm (paddle). Samples were collected at 2, 4, 6, 10, 15 & 20 minutes intervals. The amount of Ondansetron HCl released was estimated at 310 nm using UV spectrophotometer (Lab India 3000$^+$). The cumulative percentage of drug release was calculated and the data obtained was presented in the dissolution rate profiles as a function of time in (Table 3). According to the scientific literature, the amount of drug released from sublingual tablets must exceed 80% of its total content with in 15 minutes.[24]

In-vitro Drug release kinetics[25, 26]

The prepared sublingual tablets of Ondansetron HCl were subjected *in vitro* drug release kinetic studies. To

Table 2: Formulation of Ondansetron HCl sublingual tablet

Ingredients (mgs)		F1	`F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
API	Ondansetron HCl	5	5	5	5	5	5	5	5	5	5	5	5
Diluents	CP mannitol I	109.06	00	00	106.56	00	00	00	00	00	00	00	00
	CP mannitol II	00	109.06	00	00	106.56	106.56	106.56	106.56	106.56	107.18	105.93	00
	CP mannitol III	00	00	109.06	00	00	00	00	00	00	00	00	00
	Physical blend (Mannitol + Maltose + Corn Starch¬)	00	00	00	00	00	00	00	00	00	00	00	106.56
Super-disintegrants	Crospovidone	2.5	2.5	2.5	5	5	00	00	5	5	5	5	5
	Ac-Di-Sol	00	00	00	00	00	5	00	00	00	00	00	00
	Sodium starch glycolate	00	00	00	00	00	00	5	00	00	00	00	00
Bioadhesives	PVP K-30	0.625	0.625	0.625	0.625	0.625	0.625	0.625	00	00	00	1.25	0.625
	Carbopol 934	00	00	00	00	00	00	00	0.625	00	00	00	00
	Gelatin	00	00	00	00	00	00	00	00	0.625	00	00	00
Sweeter	Sodium Saccharine	0.312	0.312	0.312	0.312	0.312	0.312	0.312	0.312	0.312	0.312	0.312	0.312
Glidant	Talc	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Lubricant	Magnesium Stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25

Table 3: Summary of general dissolution conditions

Parameter	Specifications
Dissolution medium	300 ml Distilled water
Temperature	$37^0 \pm 0.5^0$c
Rotation speed	50 rpm
Volume withdrawn	10 ml at 2,4,6,10,15,20 minutes
λmax	310 nm

Table 4 : Precompression parameters of all the formulations

Formulation code	Pre-compression Evaluation Parameters				
	Bulk Density (gm/ml) (n=3) Mean±SD	Tapped density (gm/ml) (n=3) Mean±SD	Carr's Index (%) (n=3) Mean±SD	Hausner Ratio (n=3) Mean±SD	Angle of repose (n=3) Mean±SD
F1	0.561 ± 0.008	0.694 ± 0.007	19.187 ±0.645	1.237 ± 0.009	32.903 ± 0.682
F2	0.608 ± 0.005	0.763 ± 0.007	20.327 ± 0.867	1.255 ± 0.0137	38.066 ± 0.551
F3	0.559 ± 0.004	0.721 ± 0.008	22.447 ± 0.806	1.289 ± 0.013	34.070 ± 1.904
F4	0.546 ± 0.004	0.686 ± 0.007	20.295 ± 0.788	1.254 ± 0.0123	33.082 ± 1.198
F5	0.519 ± 0.004	0.660 ± 0.006	21.394 ± 0.732	1.272 ± 0.011	38.766 ± 0.853
F6	0.513 ± 0.004	0.689 ± 0.007	25.479 ± 0.752	1.342 ± 0.013	37.351 ± 1.190
F7	0.528 ± 0.004	0.682 ± 0.012	22.491 ± 0.935	1.2903 ± 0.015	32.639 ± 1.570
F8	0.534 ± 0.004	0.695 ± 0.007	23.077 ± 0.191	1.300 ± 0.003	39.591 ± 0.816
F9	0.513 ± 0.004	0.696 ± 0.007	26.314 ± 0.741	1.357 ± 0.013	39.195 ± 0.662
F10	0.567 ± 0.005	0.700 ± 0.007	19.070 ± 0.817	1.235 ± 0.012	33.91 ± 0.980
F11	0.622 ± 0.010	0.816 ± 0.018	23.723 ± 1.525	1.311 ± 0.026	31.796 ± 1.103
F12	0.525 ± 0.004	0.758 ± 0.009	30.804 ± 0.731	1.445 ± 0.015	42.806 ± 1.318

Table 5 : Post-compression Parameters of All Formulations

Formulation code	Post-compression Evaluation Parameters						
	Hardness Kg/cm2 (n=10)	Weight Variation (mg) (n=20)	Friability (%)	Drug Content (%) (n=3)	In vitro DT (sec) (n=6)	Wetting time(sec) (n=6) Mean±SD	% CDR after 15 min
F1	1.62 ± 0.13	124.4 ± 2.23	0.672	98.400 ± 0.38	55 ± 2.60	45.5 ± 1.516	88.85±0.55
F2	2.63 ± 0.18	124.9 ± 2.33	0.504	97.306 ± 0.29	88.333 ± 4.41	76.333 ± 2.422	80.02±0.60
F3	3.21 ± 0.14	124.6 ± 2.01	0.289	99.663 ± 0.14	201.833±13.48	210.167 ± 7.521	40.10±0.23
F4	1.56 ± 0.13	125.15 ± 1.72	0.580	100.252 ± 0.25	26.5 ± 1.37	31.5 ± 2.345	96.80±0.14
F5	2.48 ± 0.15	124.85 ±1.49	0.460	99.83 ± 0.38	65.166 ± 1.72	51.333 ± 2.581	96.10±0.26
F6	2.47±0.09	124.2±2.30	0.473	100.673±0.14	112.5±1.87	109.5 ± 3.016	83.92±0.39
F7	2.53±0.14	125.25 ±2.31	0.351	95.791 ± 0.38	204 ± 1.78	207.667±7.890	35.14±0.53
F8	2.42±0.12	122.9 ± 6.01	0.765	98.148 ± 0.14	74.5 ± 2.73	71.5 ± 2.509	79.32±0.73
F9	2.41±0.12	124.7 ± 1.59	0.581	100.757 ±0.25	78.5 ± 1.87	64.5 ± 3.146	95.63±0.25
F10	2.36±0.10	125.4 ± 2.52	0.198	95.538 ± 0.14	65.5 ± 2.34	45.666 ± 3.777	88.48±0.44
F11	2.66±0.09	124.9 ± 2.26	0.471	97.390 ± 0.38	75 ± 2.60	85.166 ± 3.311	78.73±0.50
F12	0.33±0.18	124.45±2.56	Breaking & Cracking tablets	99.410±0.14	64.666±2.80	40.333 ± 2.503	80.44±0.21

study the zero order release kinetics, data obtained from *in vitro* drug release studies were plotted as % cumulative amount of drug released *versus* time while for first order release rate kinetics, the data obtained was plotted as log cumulative % of drug remaining *versus* time which would yield a straight line with a slope of -nK/2.303. The results thus obtained were compared with goodness of fit test by linear regression analysis to determine drug release kinetics of developed formulation.

RESULTS AND DISCUSSIONS

Coprocessing of mannitol with maltose and Corn Starch in varying ratios was carried out and it was compared with their physical blend (formulations F5 & F12). The result obtained showed that coprocessing of excipient improves the tableting characteristics of excipient and gives out a tablet with better hardness, reduced friability & satisfactory *in vitro* drug release. Along with this coprocessing also improves precompression characteristics as better flow property, bulk density to near about 0.5 w/v which is desirable for a sublingual tablet. The tablets prepared using unprocessed physical blends fail flowability test and in case friability test chipping of tablets was observed. But tablets prepared by using coprocessed excipients with equal concentrations of other excipient showed a satisfactory flow, better hardness and a uniform *in vitro* drug release. Hardness of tablet

Table 6: Release Kinetics Profile of all formulation F-1 to F-12			
Formulation code	**Mathematical Model (r-value)**		
	Zero order kinetic	**First order kinetic**	**Results Best fit Model**
F1	0.646	0.841	First Order
F2	0.966	0.982	First Order
F3	0.970	0.984	First Order
F4	0.512	0.727	First Order
F5	0.654	0.908	First Order
F6	0.750	0.924	First Order
F7	0.969	0.989	First Order
F8	0.930	0.998	First Order
F9	0.613	0.884	First Order
F10	0.864	0.984	First Order
F11	0.922	0.990	First Order
F12	0.859	0.989	First Order

Table 7: Design constraints		
Low	**Constraint**	**Constraint**
0.000	A:CP 1	109.060
0.000	B:CP 2	109.060
0.000	C:CP 3	109.060
0.000	D:Crospovidone	5.000
0.000	E:Ac-DI-Sol	5.000
0.000	F:SSG	5.000
0.000	G:PVP K 30	1.250
0.000	H:Carbopol 934	0.625
0.000	J:Gelatin	0.625
A+B+C+D+E+F+G+H+J		112.185

increased with increase in ratio of maltose in Coprocessed excipient. But it also negatively affects disintegration time and drug release. The tablet with Coprocessed excipient with ratios of mannitol:maltose:Corn Starch 19:2:1 gave better hardness with satisfactory disintegration time and a good *in vitro* drug release. Further increase in Maltose concentration, increased hardness but resulted in decreased *in vitro* drug release & increased disintegration time. While decrease in maltose content although improved drug release and reduced Disintegration time, the tablet becomes too soft i.e. below the normal range of tablet hardness for a sublingual tablet.

Type of superdisintegrants and their ratios mainly affects the disintegration time and indirectly also affects Dissolution rate of the tablet. By comparing Formulations F5, F6, F7 it was found that tablets containing Crospovidone showed faster disintegration compared to that of tablets containing Ac-Di-Sol & Sodium starch glycolate. Ac-Di-Sol though gave better result than that of Sodium starch glycolate, but in comparison with Crospovidone it showed slower disintegration and higher wetting time. By comparing formulations F2 and F4 it was also found that, the increase in concentration of superdisintegrant reduced disintegration time and resulted in faster disintegration.

To ensure a more intimate contact of sublingual dosage form the bioadhesive polymers can be employed which posses strong bioadhesive/ mucoadhesive properties. Increasing the contact time with the sublingual mucosa with a mucoadhesive polymer improves sublingual bioavailability and result in more predictable plasma levels of the drug, leading to better therapeutic efficacy and reproducibility. The concentration and type of mucoadhesive polymer employed has significant influence on release and absorption of drug from sublingual tablet dosage form. By comparing Formulation F5, F10 and F11 it was observed that addition of a bioadhesive poly-

Table 8 : Dependent variables with their acceptable ranges for a sublingual tablet		
Dependent Variable	**Acceptable ranges**	**Goal**
Hardness	>2 Kg/cm2	Maximum
Disintegration Time	< 120 seconds	minimum
Wetting Time	< 120 seconds	Minimum
% Drug release after 15 minutes	>80% within 15 minutes	Targeted to 80%
First order release kinetic (r value)	0.9 to 0.999	In range
Weight variation	116 to 134	Targeted to 125
Content uniformity	85 to 115 %	Targeted to 100%

Table 9: Formulations of Ondansetron HCl sublingual tablet as suggested by Design Expert 8.0.7.1 (Trial Version).				
Ingredients (mgs)		FA	FB	FC
API	Ondansetron HCl	5	5	5
Diluents	CP mannitol I	0.000	5.419	17.789
	CP mannitol II	105.935	101.173	91.172
	CP mannitol III	0.000	0.000	0.000
Super-disintegrants	Crospovidone	5.000	4.996	2.572
	Ac-Di-Sol	0.000	0.000	0.000
	Sodium starch glycolate	0.000	0.000	0.000
Bioadhesives	PVP K-30	1.250	0.568	0.652
	Carbopol 934	0.005	0.029	0.000
	Gelatin	0.000	0.000	0.000
Sweetener	Sodium Saccharine	0.312	0.312	0.312
Glidant	Talc	6.25	6.25	6.25
Lubricant	Magnesium Stearate	1.25	1.25	1.25

mer to the formulation gave uniform release of drug while formulation without bioadhesive polymer showed irregular drug release pattern. Increase in concentration of bioadhesive polymers resulted in a decreased drug release. Comparison between formulations F5, F8 and F9 showed that PVP K 30 gave a better *in vitro* drug release than Carbopol 934 and Gelatin. Formulation containing Carbopol 934 fails to comply weight variation test due to its stickiness and improper die filling. Formulation containing gelatin though gave satisfactory *in vitro* drug release but residue remained after complete dissolution, which could give an unpleasent mouth feel.

Optimization of prepared sublingual tablet[26-30]

In the present work formulation Nos. 1 to 11 were tabulated in historical data mixture design 8.0.7.1(Trial Version) and based on numerical optimization the global best formulation (best values of excipients) was determined. In a mixture design, the level of a single component cannot be changed independently and the sum of the mixture components has to be equal to 100%. Ondansetron HCl (5 mg) tablets were prepared with a constant weights of various excipients like magnesium stearate (1.25 mg), talc (6.25 mg) and Sodium saccharine (0.312 mg)and the total tablet weight was kept constant (125 mg). Therefore, the experimental range lies between 0 and 112.185 mg. The restrictions imposed on the mixture component proportions are shown in (Table 7).

Experimental ranges were applied in order to comply with the relevant amounts of the same actually utilized in commercial pharmaceutical formulations. Dependent

Table 10: Comparative values of predicted and observed responses of FA, FB, FC:						
Response	Formulation A		Formulation B		Formulation C	
	Predicted Value	Observed value	Predicted Value	Observed value	Predicted Value	Observed value
Hardness	2.65	2.51±0.11	2.44	2.46±0.11	2.45	2.46±0.09
Disintegration Time	72.33	66.83±1.72	65.78	74.33±1.86	84.35	89.83±3.06
Wetting Time	80.56	57.66±1.63	58.93	46.33±2.80	71.55	85.16±3.31
% Drug release after 15 minutes	82.93	90.28	88.07	88.64	81.39	80.31
R value of First order release kinetic	0.953	0.982	0.943	0.985	0.976	0.983
Weight variation	124.86	125.05±1.63	125.01	124.65±1.75	124.699	124.7±1.97
Content uniformity	98.67	98.31±0.38	97.82	95.79±0.38	97.22	97.30±0.291

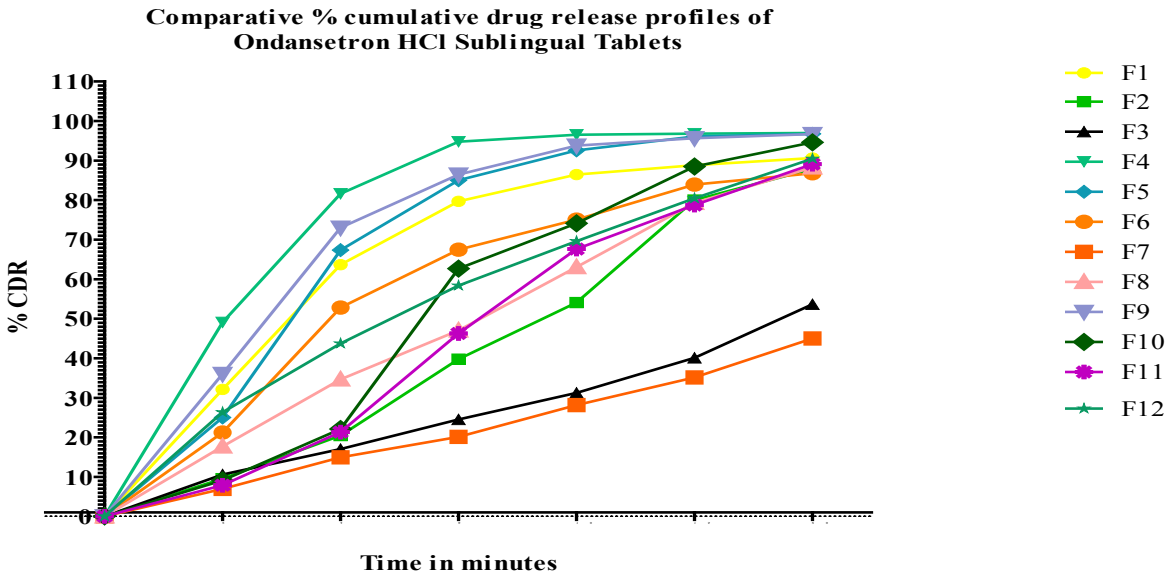

Figure 1: Comparative in vitro release profile of different formulations of Ondansetron HCl Sublingual Tablets.

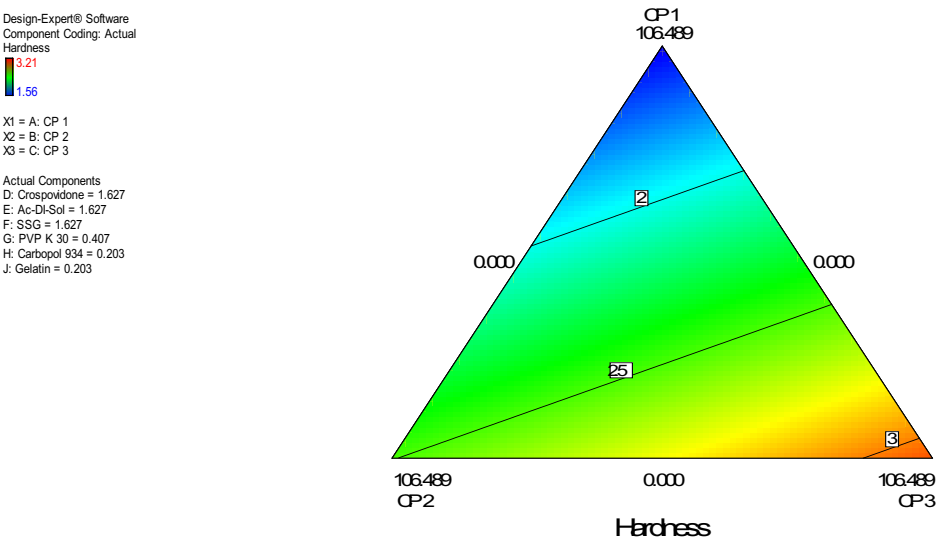

Figure 2: Hardness of tablet.

variables considered in this study were hardness, disintegration time, wetting time, % drug release, first order release kinetic, weight variation & content uniformity which are shown in (Table 8). along with their acceptable ranges for a sublingual tablet.

The formulations prepared were evaluated for precompression and post compression parameters. The data obtained was analyzed using linear model of design expert 8.0.7.1(Trial version). The response contour plots predicted from the linear model for dependent variable are shown in (Table 2-5).

Historical data mixture optimization results

The aim of the optimization was to attain the defined targets for all responses simultaneously with respect to the predefined constraints. At this stage, the defined desirable areas of all responses were superimposed and the region of interest was generated. Three formulations with high desirability were suggested in this procedure by Design expert 8.0.7.1 (Trial Version). The suggested formulations are given in Table 9. The overlay plot for three formulations suggested in optimization procedure is shown in Figure 6.

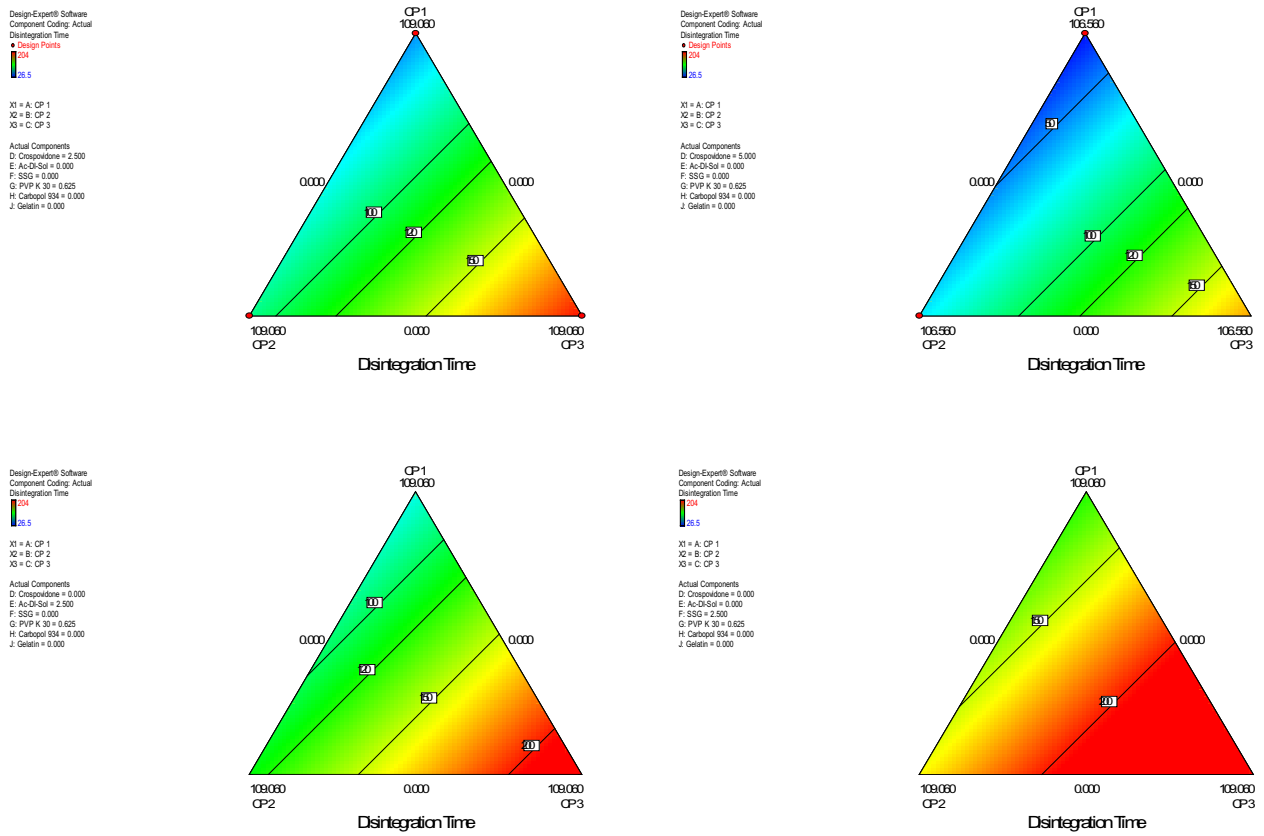

Figure 3: Disintegration Time

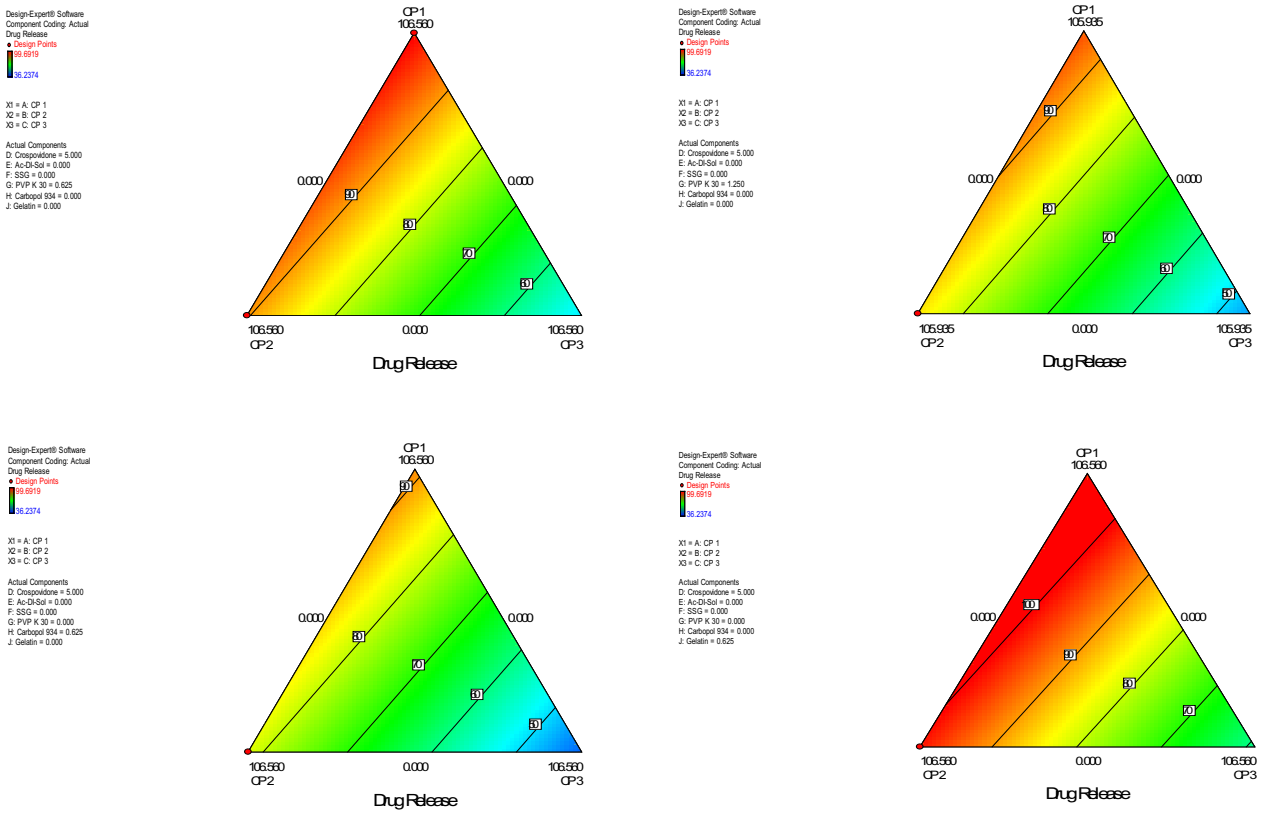

Figure 4: Percent drug release after 15 minutes

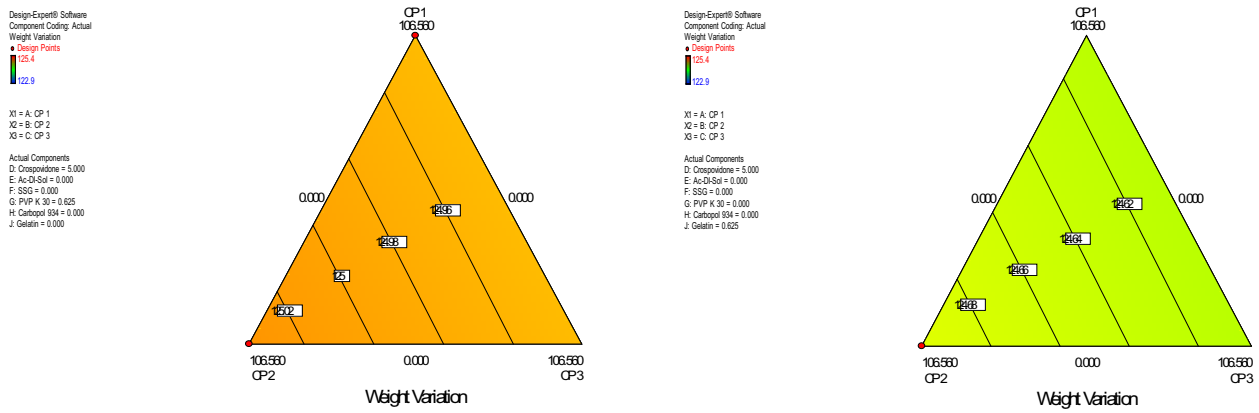

Figure 5: Weight Variation test

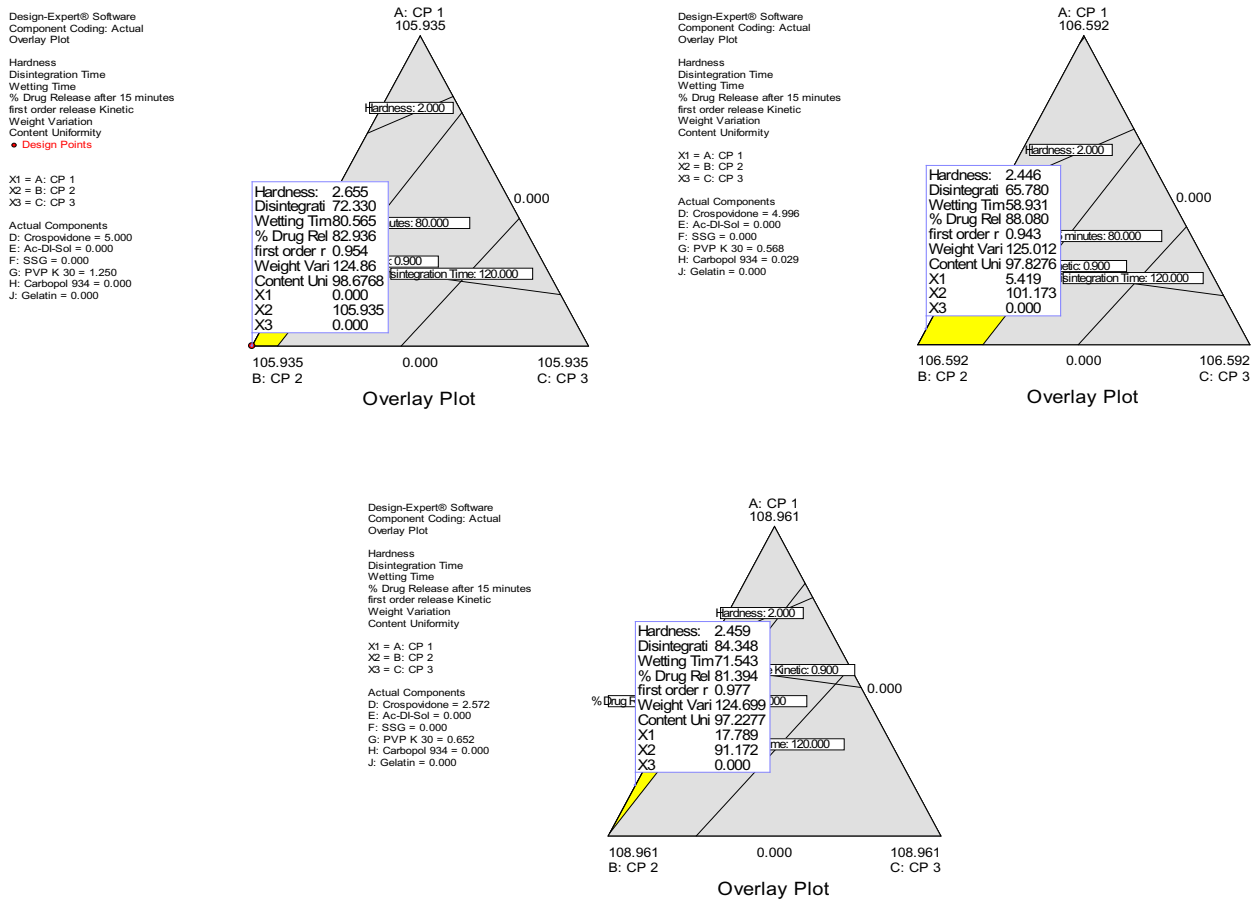

Figure 6: Formulations (A,B,C)

The observed values of responses were compared with predicted values for respective formulations by Design Expert (Trial Version 8.0.7.1). Comparative values of predicted and observed responses along with the formulation components are reported in (Table 10).

By comparing the observed values with predicted values it was concluded that among the above mentioned formulations, Formulation B shows desirable physical characteristics and also a correlation between predicted and observed results. Thus Formulation B was chosen as global best one.

SUMMARY AND CONCLUSION

The sublingual tablet containing Ondansetron HCl as a model antiemetic agent was formulated by direct compression technique using mannitol coprocessed with maltose corn starch and optimized using Historical data mixture design 8.0.7.1(Trial Version). Based upon the results obtained it was concluded that coprocessing of low compressible saccharides with high compressible saccharides improves precompression as well as post-compression characters of tablet such as flow property, compressibility, hardness, disintegration and *in vitro* drug release. Mannitol:Maltose:Cornstarch in ratio of 19:2:1 exhibited ideal sublingual tablet characteristics. Study on effect of superdisintegrants on tablet formulation proved that the use of crospovidone in a concentration of 4% gave tablets with disintegration time of less than 80 seconds while drug release of more than 80 % after 15 minutes of *in vitro* dissolution studies was observed. Addition of bioadhesive polymer into formulation helps to release the drug uniformly over period of 20 minutes. In case of prepared tablet, PVP K 30 in a concentration of 0.5% exhibited better *in vitro* drug release. Based on results of Optimization studies Formulation B prepared by using coprocessed excipient of mannitol:maltose:corn starch in ratios of 19:2:1 was adjudged as global best formulation as it established good correlation between predicted and observed values for response.

REFERENCES

1. Tripathi KD. Essentials of Medical Pharmacology. 5thEd. New Delhi: Jaypee Brothers Medical Publishers (p) Ltd; 2003. p. 7-10, 599-609.
2. Brunton LL, Parkar KL, editors. Goodman & Gillman's Manual of Pharmacology & therapeutics. NY: The McGraw-Hill; 2008. p. 644-50.
3. Tuca A. Use of granisetron transdermal system in the prevention of chemotherapy-induced nausea and vomiting: A review. Cancer Management and Research. 2010; 2: 1-12.
4. Eunsook C, Hyesun G, Inkoo C. Formulation and evaluation of ondansetron nasal delivery systems. Int J Pharm. 2008; 349(1): 101-7.
5. Fumoleau, Giovannini M, Rolland F, Votan B, Paillarse JM. Ondansetron Suppository: an Effective Treatment for the Prevention of Emetic Disorders Induced by Cisplatin-based Chemotherapy. Oral Oncol. 1997; 33(5): 354-8.
6. Zempsky, William T. Alternative Routes of Drug Administration--Advantages and Disadvantages. Pediatrics. 1997 July 1; 100(1): 143-53.
7. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci. 2011; 3(2): 18-22.
8. Leilani Lea. Sublingual Absorption. [Online]. 1996 July 13 [cited 2012 oct 18]; [6 screens] Available form: URL: http://www.positivehealth.com/article/colon-health/sublingual-absorption
9. Nibha KP, Pancholi SS. An Overview on: Sublingual Route for Systemic Drug Delivery. Ijrpbsonline. 2012 Apr-Jun; 3(2): 913-23.
10. Norman AA. Tablet Manufacture by Direct Compression. In: James S, editor. Encyclopedia of pharmaceutical technology. Vol 2 New York (NY): Informa Healthcare USA, Inc; 2007. p. 3674.
11. Bansal AK, Nachaegari SK. Co-processed excipient for solid dosage form. Pharm Technol. 2004 Jan; 28(1): 52-64.
12. William RP, Tapash KG. Intraoral Delivery Systems: An Overview, Current Status, and Future Trends. In: James S, editor. Drug Delivery to the Oral Cavity: Molecules to Market. Boca Raton, FL CRC Press Taylor & Francis Group; 2005. p. 1-40. (DRUGS AND THE PHARMACEUTICAL SCIENCES; vol 145).
13. Raymond CR, Paul JS, Sian CO, editors. Handbook of pharmaceutical excipients. Great Britain: The Pharmaceutical Press; 2006. p. 447-53, 725-30.
14. Peter D. Oral Solid Dosage Forms. In: Mark Gibson, editor. Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage. 2nd ed. New York (NY): Informa Healthcare USA, Inc; 2009. p. 367-75.(Drugs And The Pharmaceutical Sciences A Series of Textbooks and Monographs; vol 199)
15. United State Pharmacopeia 30-National Formulary 25 [CD ROM]. The United States Pharmacpeial Convention, Inc; 2007: 276, 643, 2426.
16. British pharmacopeia 2007 [CD ROM]. Vol IV Appendices XVII H. Resistance to Crushing of Tablets *(Ph. Eur. method 2.9.8)*.
17. Kalaichelvi R, Madhava B, Manikanta S, Gopinath G, Usha M, Venkataramana D, *et al.* UV spectrophotometric method for determination of Ondansetron Hydrochloride in pure and its formulation. Int J Pharm Pharm Sci. 2012; 4(4): 151-2.
18. Finkel R, Clark MA, Cubeddu LX. Lippincott's Illustrated Reviews: Pharmacology. 4thed. Philadelphia, (PA): Lippincott Williams & Wilkins; 2009. p. 337-9.
19. British pharmacopeia 2007 [CD ROM]. Vol I & II. Monographs: Medicinal & Pharmaceutical Substances. Ondansetron Hydrochloride Dihydrate.(*Ph Eur monograph)*.
20. Nagendrakumar D, Raju SA, Shirsand SB, Para MS. Design of fast dissolving Granisetron HCl tablets using novel co–processed superdisintegrants. J Biosci Tech. 2009; 1(1): 8-14.
21. Government of Indian Ministry of health, Indian Pharmacopeia. The controller of publication, New Delhi. 2007; 1: 175-88.
22. Bhanja SB, Ellaiah P, Roy HK, Samal BK, Tiwari S, Murthy KVR. Formulation and evaluation of Perindopril Sublingual Tablets. Ijrpbs online. 2011 Jul-Sept; 2(3): 1193-8.
23. Bhardwaj V, Shukla V, Goyal N, Salim MD, Sharma PK. Formulation and evaluation of fast disintegrating sublingual tablets of Amlodipine Besylate using different superdisintegrants. Int J Pharm Pharm Sci. 2010; 2(3): 89-92.
24. Tas C, Bayrak Z, Tasdemir U, Erol H, Ozkan CK, Savaser A, et al. Formulation of Zolmitriptan sublingual tablets prepared by direct compression with different polymers: *In vitro* and *In vivo* evaluation. Eur J Pharm Biopharm. 2011; 78(3): 499-505.
25. Dash S, Padala NM, Lilakanta N, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica n Drug Research. 2010; 67(3): 217-23.
26. Noushin BB, Naghmeh H, Seyed MF, Bijan S. Formulation and optimization of Captopril sublingual tablet using D-Optimal Design. Iran J Pharm Res. 2008; 7(4): 259-67.
27. Sharma RN, Pancholi SS. Optimization techniques in pharmaceutical industry: A Review. J Current Pharm Res. 2011; 7(1): 21-8.
28. Dalavi VV, Patil JS. Optimization techniques: An introductory overview. J Pharm Res. 2009 Feb; 2(2): 144-7.
29. Narendra C. Review on design of experiment and optimization. VIPS, Bangalore. 2006; volume and issue missing? 1-21.
30. Noushin B, Naghmeh H, Seyed MF, Bijan S. Development and Optimization of a sublingual tablet formulation for physostigmine salicylate. Acta Pharm. 2009; 59(3): 301-12.