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FORMULATION AND EVALUATION OF LIQUISOLID COMPACT OF CHLORTHALIDONE

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ABSTRACT

Liquisolid compacts were used to formulate water insoluble drugs in non-volatile solvents and converting into acceptably flowing and compressible powders. The main objective of present investigation was to enhance the dissolution rate of poorly water soluble drug Chlorthalidone by using liquisolid technique. Several liquisolid tablets were prepared by using different carrier materials such as microcrystalline cellulose (Avicel pH-102) and coating material such as Aerosil respectively. Polyethylene glycol 400 was used as nonvolatile water miscible liquid vehicle. The liquid loading factors for such liquid vehicle was calculated to obtain the optimum amounts of carrier and coating materials necessary to produce acceptable flowing and compactable powder admixtures viable to produce compacts. Before compression, powdered mass were evaluated for various parameters like flow properties, content uniformity etc. All the prepared formulations were compressed using 13mm punch after addition of 5 % Sodium starch glycolate and crospovidone to each formulation. The formulated liquisolid tablets were evaluated for post compression parameters such as weight variation, hardness, drug content uniformity,percentage friability and disintegration time. The in-vitro release characteristics of the pure drug, drug from marketed tablets (as reference) and liquisolid technique (test sample), were studied. DSC study was performed to check drug excipients compatibility. The spectra revealed that there was no interaction between drug and excipients.The results showed that liquisolid formulations of Chlorthalidone exhibited higher percentage of drug release than marketed formulation.

Keywords: Chlorthalidone, Sodium starch glycolate and crospovidone.

INTRODUCTION

Solubility is one of the most important physicochemical properties of any drug because lowsolubility can affect the bioavailability of orally administered dosage forms. Thus, it is veryimportant to enhance the solubility of a poorly soluble drug. For absorption, a drug must bepresent in the form of an aqueous solution at the site of absorption. Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastro intestinal tract.[1]

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability.[2]Solving solubility problems is a major challenge for the pharmaceutical industry with development of new pharmaceutical products, since nearly half of the active substances being identifiedthrough the new paradigm in highthroughput screening are either insoluble or poorly soluble in water.[3,4]

Nearly one-third of drugs in development arewater insoluble and one-half fail in trials because of underprivileged pharmacokinetics.[5] These poorly water soluble drugs are

alliedwith slow drug absorption leading toinadequate and variable bioavailability andgastrointestinal mucosal toxicity of drugs.[6] Various methods employed to improve the dissolution characteristics ofpoorly water soluble drugs are solubilization, pH adjustment, cosolvancy, microemulsion, self emulsification, polymeric modification, drug complexation, and micronization, use of surfactant as a solubilizing agent, the prodrug approach and solid dispersion. The new technique developed by Spireas 'liquisolid system' is the most promising method for improving the dissolution properties of poorly solubledrugs.[7]

A liquisolid system refers to formulations formed by conversion of liquiddrugs, drug suspensions or drug solution innon-volatile solvents, into dry, non-adherent,free- flowing and compressible powdermixtures by blending the suspension orsolution with selected carriers and coatingmaterials.[3] Drug presentin the liquid medicament in liquisolid system is in the solubilised or molecularly dispersedstate, so the dissolution can be enhanced by increased surface area and betterwetting properties.[8] The technique of liquisolid compacts has been successfullyemployed to improve the in vitro release of poorly water soluble drugssuch as carbamazepine, Atorvastatin calcium, famotidine, Piroxicam, Indomethacin, Rofecoxib, Carvedilol, Irbesartan etc. The advantages of Liquisolid techniques includes simplicity, low cost and capability of industrialproduction.[9-16]

Chlorthalidone is used to treat high blood pressure and fluid retention caused by various conditions, including heart disease. Chlorthalidone is a phthalamide derivative of benzene sulphonamide and is designated as 2- chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulphanilamide. Chlorthalidone is widely accepted for its excellent antihypertensive and anti-diuretic effect.Chlorthalidone is considered first-line therapy for management of uncomplicated hypertension as there is strong evidence from meta-analyses that thiazide diuretics such as chlorthalidone reduce the risk of stroke, myocardial infarction, heart failure, and cardiovascular all-cause mortality in patients with hypertension.[18]Chlorthalidone is BCS IV drug which is poorly soluble in water (0.986mg/L). It is rapidly absorbed after oral administration with peak plasma concentration at 30 to 60 min.

MATERIALS AND METHODS

Chlorthalidone and microcrystalline cellulose (AvicelPH 102)were received as gift samples from Medley Pharmaceutical Ltd., Daman. Aerosil 200 was obtained as gift sample from Yarrow Chem Products, Mumbai. Sodiam starch glycolate, Crospovidone, Mannitol,PEG 400, 300 and 600, Tween 20, Tween 80 were purchased from S D Fine Chem. Products, Mumbai. All other excipients and reagents used were of pharmaceutical grade.

PREFORMULATION STUDY

Drug excipients compatibility (FTIR)

Fourier transform infrared spectroscopy was employed to characterize further the possible interactions between the drug and the formulation excipients by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1} with a resolution of 4 cm^{-1}.

Solubility studies[17]

The saturation solubility studies were carried out in different non volatile solvents shown in Table-1 i.e. PEG 400, PEG 600, Propylene Glycol (PG), Tween 20, Tween 80, so as to select the best non volatile solvent for preparation of liquid medication. In brief, excess amount of Chlorthalidone was mixed with non-volatile solvents separately in 50ml vials. The mixtures were shaken on shaker for 48 hours. Then solutions were filtered through 0.45µ membrane filter and diluted suitably with 1% sodium lauryl sulphate (SLS) and analyzed UV spectrophotometrically (UV 1700, Shimadzu, Japan) at 275 nm for their drug content. Three determinations were carried out for each sample to calculate the solubility of Chlorthalidone.

Measurement of Angle of Slide[18]

This experiment was designed to measure the flowable liquid retention potential (φ-value) for Avicel PH 102 (carrier material) and Aerosil (coating material) and the optimum liquid load factor. The φ-value of a powder is the maximum amount of given non-volatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability, whereas is the mass ratio (w/w) of the liquid medication to the carrier powder in the liquisolid formulation. Powder admixtures containing 5 g of either carrier or coating with increasing quantity of nonvolatile liquid vehicle were mixed using a mortar and pestle. Each admixture was then placed on a shiny metal plate; the plate was then tilted until the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide (θ). The flowable liquid retention potential was calculated using the following equation:

$$\varphi\text{-Value} = \frac{\text{Weight of nonvolatile liquid}}{\text{Weight of carrier or coat}} \quad \textbf{(1)}$$

Each admixture has specific φ-values which were determinedand plotted against respective measured angle of slide for allnonvolatile liquid vehicles. The φ-value that corresponds toan angle of slide of 33° was reported to represent the flowableliquid retention potentials of powder admixtures.

Preparation of Preliminary batch formulation

The appropriate amounts of carrier and coatingmaterials used for each formulation depend upon $Lf$of thatformulation (Table-2). The liquid load factor (Lf) is calculated by using following formula

Lf = ϕ + ø (1/R) (2)
Lf =W/Q (3)
R=Q/q (4)

Where, ϕ and ø are the values of the carrier and the coating powders respectively while R is excipients ratio.

Liquisolid tablets of Chlorthalidone were prepared using composition mentioned in Table-3. Chlorthalidone and non-volatile solvent were accurately weighed in 25 ml glass beaker and then sonicated until homogenous solution was obtained. The medication was incorporated into calculated quantity of carrier and coating material so liquisolid blend was obtained. The liquisolid powder was further blended with mannitol and 5% SSG and Crospovidone for 5 min and 1% magnesium stearate and Talc were added in the polybag just before compression. Liquisolid compacts blend were compressed using tablet compression machine.(Rimek, Karnavati Engineering,India) using flat-faced punch with a compression force thatprovide acceptable tablet hardness.

QbD-DoE approach for 3^2 full factorial design formulations

On the basis of preliminary studies a 3^2 full factorial design was used to determine the effects of independent variables X_1(Concentration of Chlorthalidone in non-volatile liquid PEG-400) and X_2(Carrier: coating ratio) on dependent variablesDisintegration time, % release of drug after 15 minute and 30 minutes. The selection of dependent and independent variables is given in Table-3.

$Y=b0+ b1X1 + b2X2 + b12X1X2 + b11X1\ 2+ b22X22$ (5)

Where Y is the measured response associated with each factor level combination; to intercept b0; regression coefficients b1 and b2 are computed from the observed experimental values of Y; and X1 and X2 are the coded level of independent variables. The terms X1 and X2 represent the interaction and quadratic terms respectively. The selected independent and dependent variables are shown in table along with their low (-1), medium (0) and high (+1) level, which were selected based on the results from preliminary experimentation and literature survey. A design matrix comprising of 9 experimental runs was constructed as shown in table. The concentration of drug in liquid (X1) and carrier: coating ratio (X2) is used to prepare the 9 formulations according to the experimental design.

Precompression Studies

Angle of Repose

The angle of repose of powder blend wasdetermined by fixed height funnel method. Angle of repose(θ) was calculated using the following equation:

$$\theta = \tan^{-1}\frac{h}{r} \quad \textbf{(6)}$$

where$h$ and r are the height and radius of powder cone.

Compressibility Index

The compressibility index of thepowder blendwas determined byCarr's compressibility indexas per equation

$$\text{Carr's index} = \frac{[(\text{Tapped density} - \text{Bulk density}) \times 100]}{\text{Tapped density}} \quad \textbf{(7)}$$

Hausner's Ratio

Hausner's ratio was calculated by following formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \textbf{(8)}$$

Evaluation of Compressed Tablets

Hardness

The hardness of the tablets was determined Using pharmatest hardness tester. It is expressed in kg/cm^2.

Friability Test

Roche friabilator (Electrolab) was used for friability test of tablets.

Disintegration Time
The disintegration time of the tablets was measured in distilled water (37 ± 2 ℃) using disintegration test apparatus (Electrolab, India).

Content Uniformity
Five tablets were powdered, and 20mg equivalent weight of Clorthalidone was accurately weighed and transferred into a 100mL volumetric flask. Initially,10mL of methanol was added and shaken for 10min.Then, the volume was made up to 100mL with distilled water. The solution in the volumetric flask was filtered, diluted suitably, and analyzed spectrophotometrically at 275 nm using UV-visible double beam spectrophotometer (UV1800, Shimadzu, Japan).

In-Vitro Drug Release Study
The *in vitro drug* releasestudy of the tablets was performed using USP type IIapparatus at 37 ℃ ±0.5 ℃using distilled water (900 mL) as a dissolutionmedium and 50 rpm. At the predetermined time intervals,10mL samples were withdrawn and replaced with freshdissolution media.Withdrawn samples were filtered througha 0.45μm membrane filter, diluted, and assayed at 275 nm using a ShimadzuUV-1800 double-beam spectrophotometer.

RESULTS AND DISCUSSION

Drug excipients compatibility study

Fourier Transform Infrared Spectroscopy (FT-IR)
The FT-IR spectra of Chlorthalidone and physical mixture of drug and excipients are shown in Figure-1. The prominent peaks of drugs was obtained at, 1101, 1690, 1713, and 1062 cm^{-1} and the prominent peaks of Avicel PH 102 and Aerosil were observed at 2884, 1423, 1530 and 1102.51, 1062.60 cm^{-1} respectively. All the prominent peaks of drug and excipients were present in the IR spectra of physical mixture indicating the physical compatibility between excipients and drug.

Solubility Study of Chlorthalidone
Solubility data of drug Chlorthalidone in various liquid vehicles is shown inTable-1.Chlorthalidone appears to be more soluble in PEG 400 (11.65 ± 0.135 mg/ml) than other liquids. The solubility is an important factor in liquisolid systems, as higher solubility of drug in liquid vehicle can lead to higher dissolution rates since the drug will be more molecularly dispersed and more surface of drug will be exposed to the dissolution media.

Measuring Angle of Slide
Angle of slide determination isan important step in the formulation of liquisolid tablets. The relationship of angle of slide with corresponding φ of Avicel for Aerosil is shown in Figure-2. The φCa and φCo for liquid vehicles were used to calculate Lf. The $Lf$was then used to decide the optimum amount of carrier and coating materials required to ensure dry-looking, free-flowing and compactible powdered systems. The lowest liquid factor was obtained for Avicel PH 102 shown in Table-2.

Precompression Studies
Powder flowability is crucial in the industrial production of tablet dosage forms, as a uniform powder stream through hopper confirms uniformity of both tablet weight and drug content. The results of various flow parameters are shown in Table-4.

Quality Control Studies
All prepared tablets complied with the pharmacopoeial required specifications for the weight variationand content uniformity tests. Results of hardness, friability, disintegration time and drug content are represented in Table-4. Hardnesstest showed an average hardness of liquisolid tablets ranging from 4.3 ± 0.3 to 4.6 ± 0.4Kg/cm^2. Another measure oftablets strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally consideredacceptable.The percentage friability for all formulations wasbelow1%, indicating that the friability iswithin the prescribedlimits. This indicates acceptable resistance was shown by liquisolid tablets to withstand handling. Disintegration timewas found to be in the range of 21±1.16 to 294±3.03 seconds for liquisolid preparations intended for immediate drug release characteristics.

In-vitro dissolution
The results of in vitro percentage of drug released at different time intervals plotted against time to obtain therelease profile shown in Figure-3. All the liquisolid compacts showed higher drug release than the pure drug. The initial rapid drug release from liquisolid formulation may be due to the use of super-disintegrant which causes a faster de-aggregation process leaving the liquisolid particles in the aqueous environment
The results showed thatthere was significant difference between the release profile of the pure drug and all the liquisolid compacts. Theenhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that, the drug isalready in

solution in PG, while at the same time, it is carried by the powder particles. Thus, its release is accelerated due to its markedly increased wettability and surface availability tothe dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanismsfor explaining the enhanced dissolution rate from the liquisolid compacts. The release from all batches appeared immediate release. The batches CL4, CL5and CL9 showed>80 % drug release within 45 minutes. The results revealed that, when 10% difference of carrier and coating material ratio showed good dissolution of drug.
To determine the effect of independent variables on the dissolution, 3^2 factorial design was applied. The observation response for 9 formulation prepared were fit simultaneously to quadratic model using 9.0.2 design expert. The comparative value of R2 , adjusted value R2 , predicted R2 , adequate precision and % CV are given by the quadratic model along with regression equation generate for individual response is given below. From the factorial equation (Equation. 9-11), it can be concluded that the enhancement of drug release is dependent on both the factors under consideration. The carrier: coating concentration is positively influencing the solubilization as it provides surface area for dissolution. It can be observed that more is the carrier: coatingratio better is the solubilization. The reasons behind the effect may be the availability of greater effective surface area due to more concentration of carrier. Less coat concentration imparts less hydrophobic characters to dosage form. Drug concentration in the liquid medication shows negative effect on the dissolution property. This may be because of availability of more amount of solvent for better solubilization of drug.

$$Y1= 82.47+34.50X1-139.50X2-28.50X12+14.30X11+73.10X22 \quad (9)$$

$$Y2= 70.12-8.44X1+15.01X2-1.85X12-0.54X11-5.60X22 \quad (10)$$

$$Y3= 79.68-4.80X1+14.65X2-1.40X12+3.39X11-10.55X22 \quad (11)$$

The effect that favours the optimization that was represent in +ve values and the relationship between factor and response represent in –ve values not favours the optimization. Table-7 shows the effect of drug concentration in PEG 400(X1) and carrier: coating material ratio (X2) has the effect onresponse, disintegration time, t15 and t30.
Thedatain Table-8 demonstrated that Y1 and Y3 dependent variable were significant at 5% level of P values were < 0.05. The predicted value R2 is reasonable agreement with adjusted model discrimination. The % CV is < 10% for Y1 and Y2 model which shown that model are reproducible.

Comparison of dissolution data of optimized formulation and conventional formulation

It is shown in figure-5 that the optimized formulation (OCL9) has higher dissolution rate compare to marketed formulation (CLS). The optimized formulation releases 82.59 % drug in 45 minute whereas marketed formulation releases 64.80% drug after 45 minute. The liquisolid technique brings about a faster dissolution by different proposed mechanisms of solubility enhancement which include phenomenon of drug being in the dissolved or molecularly dispersed state as well as absorption and adsorption of liquid medication in the internal structures of hydrophilic carrier material providing a greater effective surface area required for the mass transfer of drug molecules from adsorbed and absorbed liquid medication phase to the bulk of dissolution medium.The second mechanism is the co-solvency between the non-volatile hydrophilic solvent and water.

CONCLUSION

The purpose of the present study was to formulate the liquisolid system of Chlorthalidone for better dissolution rate accompanied by acceptable flow and compression characteristics. In this investigation, preformulation study was performed for authentication of drug and determination of drug solubility. Clorthalidone liquisolid tablet CL9 formulated from 30%w/w of PEG to the drug was found to be superior in terms of dissolution properties in comparison with other liquisolid formulations. Finally, it can be concluded that, liquisolid formulation containing Chlorthalidone with Avicel as carrier and Aerosil as coating material is efficient to enhance the drug dissolution rate with acceptable flow and compression characteristics. Thus, liquisolid approach has potential application for formulation research in improvement of dissolution rate of Chlorthalidone.

Table 1: Study of solubility in non-volatile oil

Non volatile Solvent	Solubility (mg/ml)
Polyethylene glycol 400	11.65 ± 0.135
Polyethylene glycol 600	6.17 ± 0.158
Polyethylene glycol 300	4.76 ± 0.140
Propylene glycol	4.49 ± 0.085
Tween 80	4.84 ± 0.014
Tween 20	4.10 ± 0.115

Table 2: Liquisolid formulation parameters for powder excipients

Powder excipients	Φ- values PEG 400	Ψ-number PEG 400
Avicel PH102	0.005	0.242
Aerosil	3.26	0.653

Table 3: Formulation of liquisolid tablets

	Formulation Batches								
	CL1	CL2	CL3	CL4	CL5	CL6	CL7	CL8	CL9
X1	10	20	30	10	20	30	10	20	30
X2	10	10	10	20	20	20	30	30	30
Load factor (Lo)	0.307	0.307	0.307	0.168	0.168	0.168	0.112	0.112	0.112
Avicel	0.325	0.162	0.108	0.595	0.297	0.196	0.892	0.446	0.294
Aerosil	0.0325	0.0162	0.0108	0.0297	0.0149	0.0098	0.0297	0.0148	0.0098
Mannitol	10	10	10	10	10	10	10	10	10
SSG	5	5	5	5	5	5	5	5	5
Crospovidone	5	5	5	5	5	5	5	5	5

* Talc and magnesium stearate were used in concentration of 1% w/w

** X1 Concentration of Chlorthalidone in non-volatile liquid PEG-400 (-1)-10, (0)-(20), (+1)-(30), X2= Carrier: coating ratio

*** Y1 = Disintegration time, Y2 = % release of drug after 15 minute, Y3 = % release of drug after 30 minute

Table 4: Characterization of powder mixtures

Batches	Angle of repose (˚)	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio
CL1	33.21±2.0	0.32±0.08	0.49±0.09	34.69	1.53
CL2	32.61±1.3	0.27±0.08	0.43±0.06	37.20	1.59
CL3	32.0±0.87	0.34±0.02	0.52±0.02	32.69	1.48
CL4	36.75±0.9	0.50±0.07	0.71±0.06	29.57	1.42
CL5	29.68±1.1	0.41±0.06	0.52±0.08	21.15	1.26
CL6	33.0±1.00	0.36±0.02	0.61±0.06	40.90	1.68
CL7	20.76±0.80	0.42±0.06	0.53±0.04	20.76	1.25
CL8	27.9±1.2	0.39±0.09	0.57±0.03	31.57	1.46
CL9	30.11±1.1	0.41±0.06	0.52±0.02	21.15	1.26

Table 5: Physical properties of liquisolid tablets

Batches	Disintegration Time (Sec)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
CL1	247±0.84	4.3 ± 0.3	0.22	97.56±1.92
CL2	294±3.03	4.5 ± 0.4	0.43	99.43±0.53
CL3	372±2.65	4.4 ± 0.2	0.47	99.31±1.28
CL4	64±1.80	4.6 ± 0.4	0.30	99.8±1.26
CL5	75±2.01	4.5 ± 0.3	0.44	98.00±2.02
CL6	136±2.08	4.5 ± 0.4	0.80	97.26±1.71
CL7	24±3.68	4.4 ± 0.4	0.91	99.4±0.63
CL8	31±2.37	4.6 ± 0.4	0.58	97.82±2.03
CL9	21±1.16	4.4 ± 0.4	0.30	98.54±0.78

Table 6: 3^2 design layout with respective observed responses

Batches	X1 drug concentration in PEG-400	X2 Carrier: Coating ratio	Y1 Disintegration time (sec)	Y2 (drug release at 15min) (%)	Y3 (drug release at 30min) (%)
CL1	-1	-1	247	44.19	54.73
CL2	0	-1	294	63.72	71.46
CL3	+1	-1	372	48.02	55.51
CL4	-1	0	64	59.85	79.2
CL5	0	0	75	61.00	72.00
CL6	+1	0	136	47.52	55.49
CL7	-1	+1	24	49.95	63.40
CL8	0	+1	31	47.52	58.49
CL9	+1	+1	21	68.40	77.80

Table 7: Summary of results

Y	P value	R^2	Adjusted R^2	Predicted R^2	Adequate Precision	%CV	Press
Y1	0.0002	0.9985	0.9961	0.9863	52.88	5.86	1894.28
Y2	0.0733	0.9185	0.7826	0.0157	7.751	11.22	1989.30
Y3	0.9927	0.9927	0.9805	0.9246	23.47	2.71	127.48

Table 8: results of multiple Y1, Y2 and Y3

Dependent variables	Y1 = Disintegration time, R^2= 0.9985		Y2 = t15 min, R^2=0.9185		Y3= t30 min, R^2= 0.9927	
	P value	Coefficients	P value	Coefficients	P value	Coefficients
Intercept	0.0002	82.47	0.0733	70.12	0.0021	79.68
X1	0.0020	34.50	0.0685	8.44	0.0102	4.80
X2	0.0001	139.50	0.0157	15.01	0.0004	14.65
X12	0.0062	28.50	0.6519	1.85	0.2613	1.40
X11	0.0916	14.30	0.9244	0.54	0.0994	3.39
X22	0.0011	73.10	0.3632	5.60	0.0052	10.55

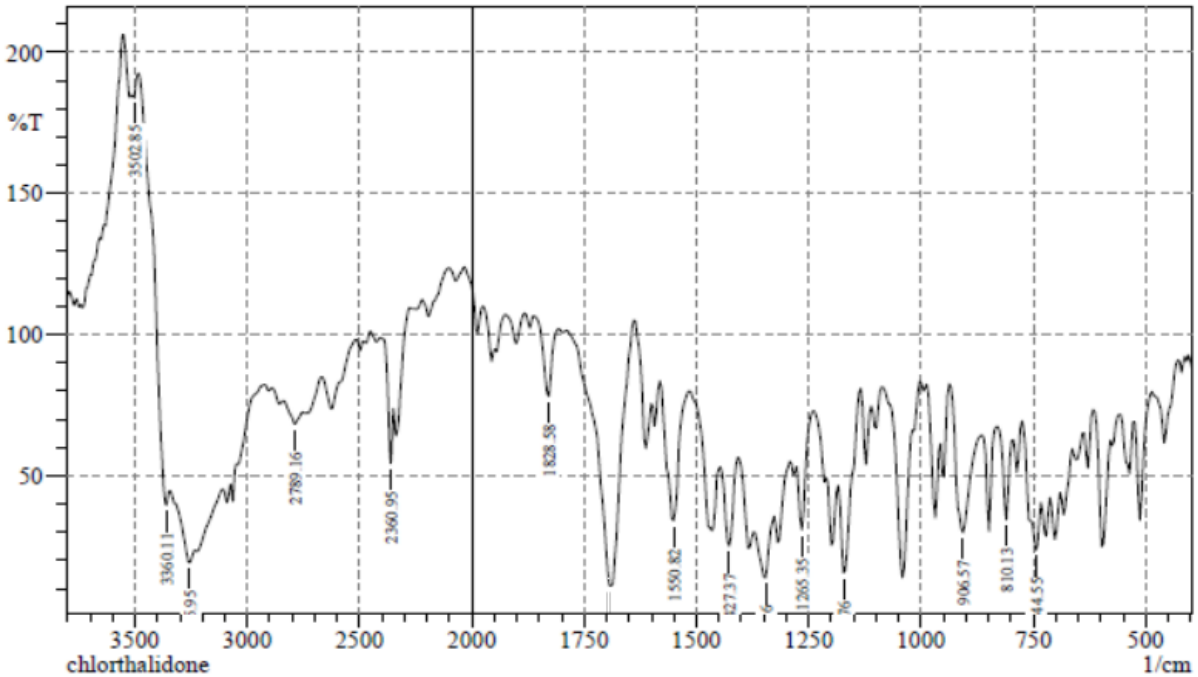

Fig. 1A: IR spectrum of Chlorthalidone (pure drug)

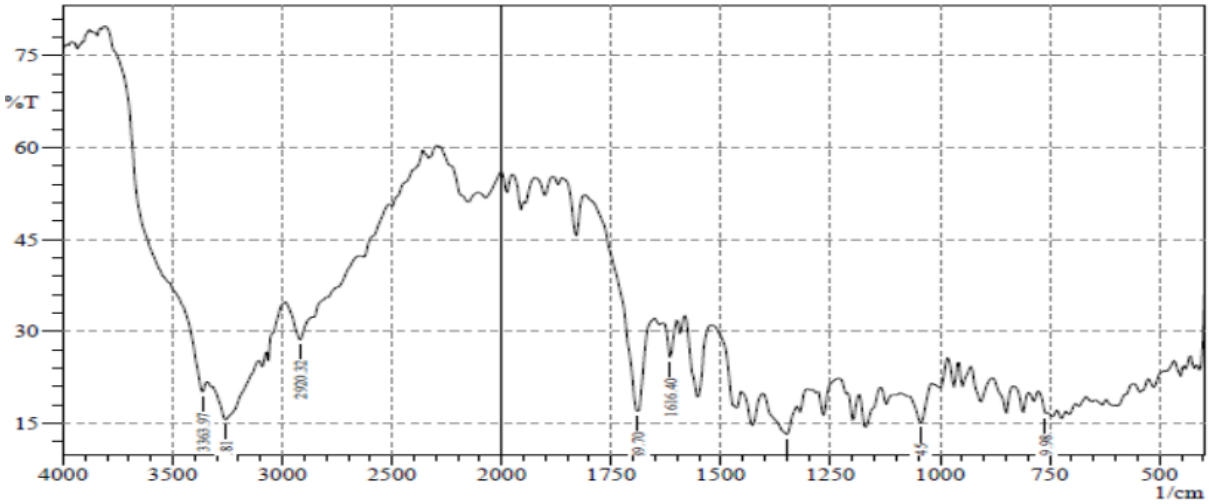

Fig. 1B: IR spectrum of physical mixture of Chlorthalidone and excipients

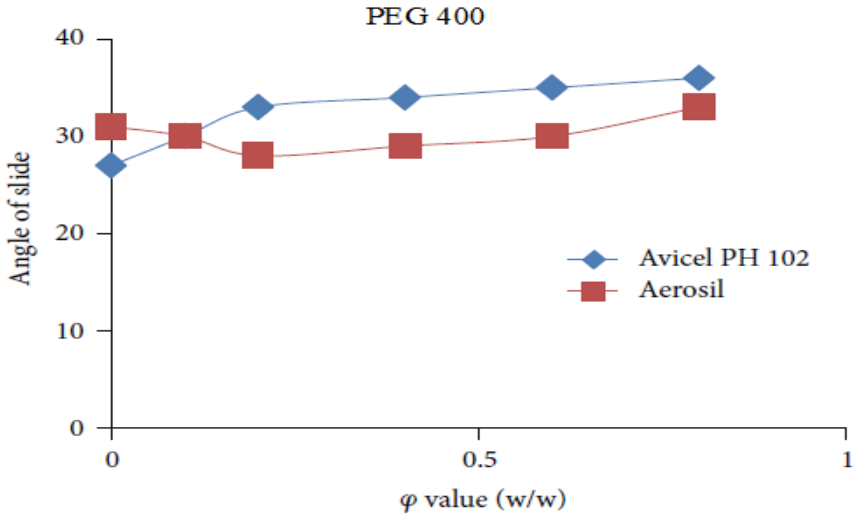

Fig. 2: The angle of slide of Avicel and Aerosil with PEG 400

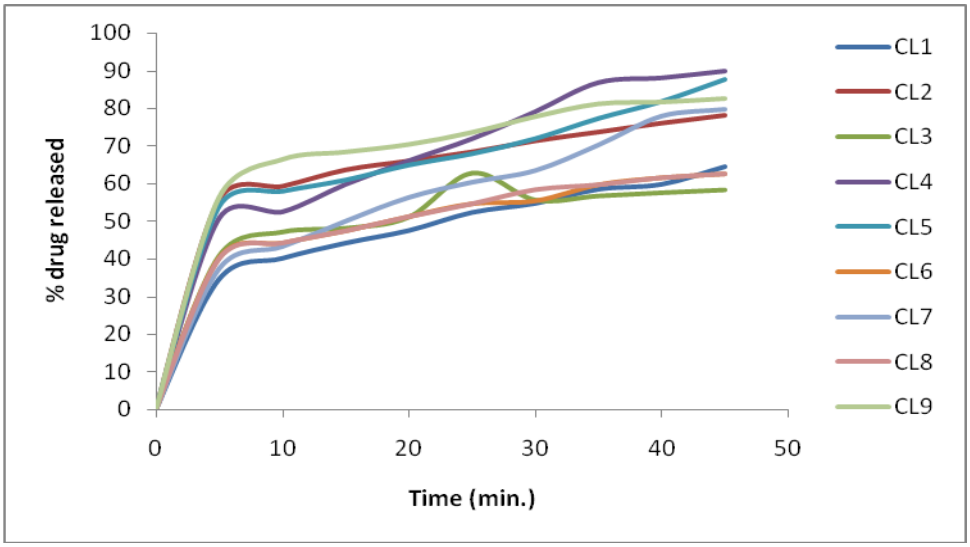

Fig. 3: *In-vitro* drug release profile

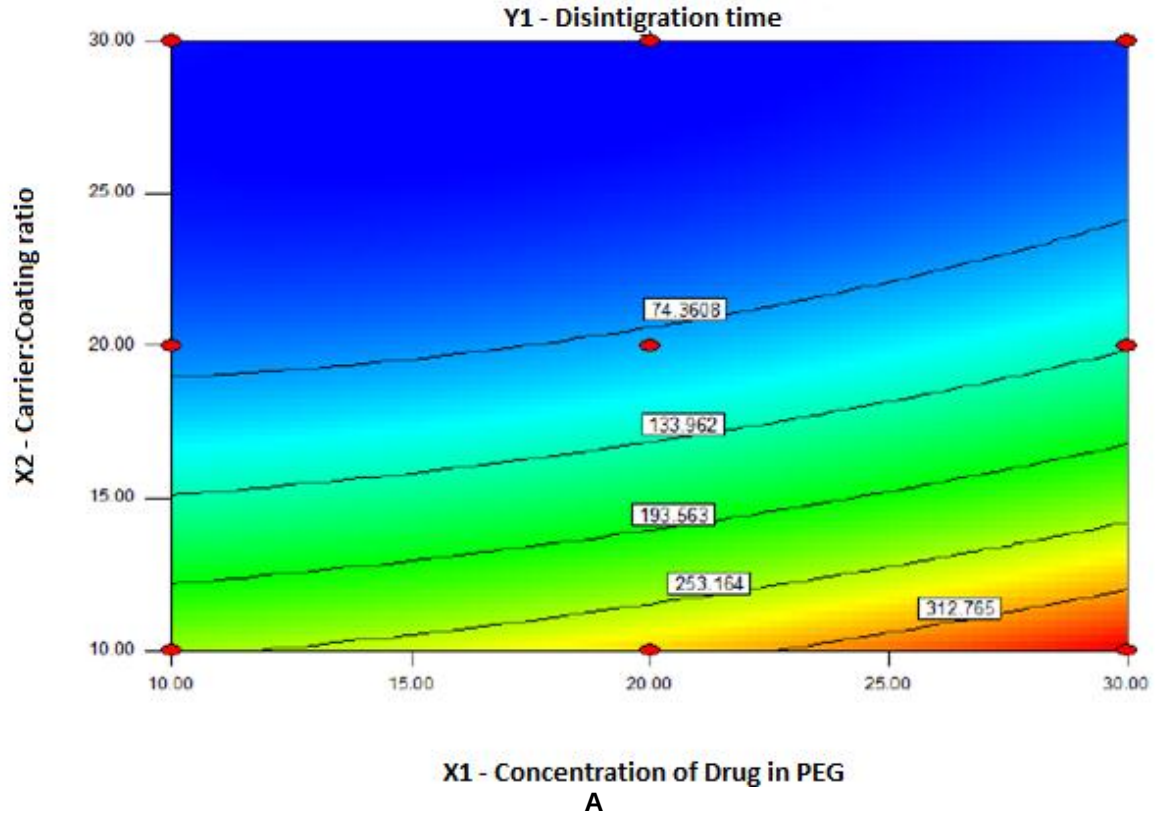

Fig. 4: (A)-Contour plot and (B) 3-D response surface plot for Disintegration time Y1

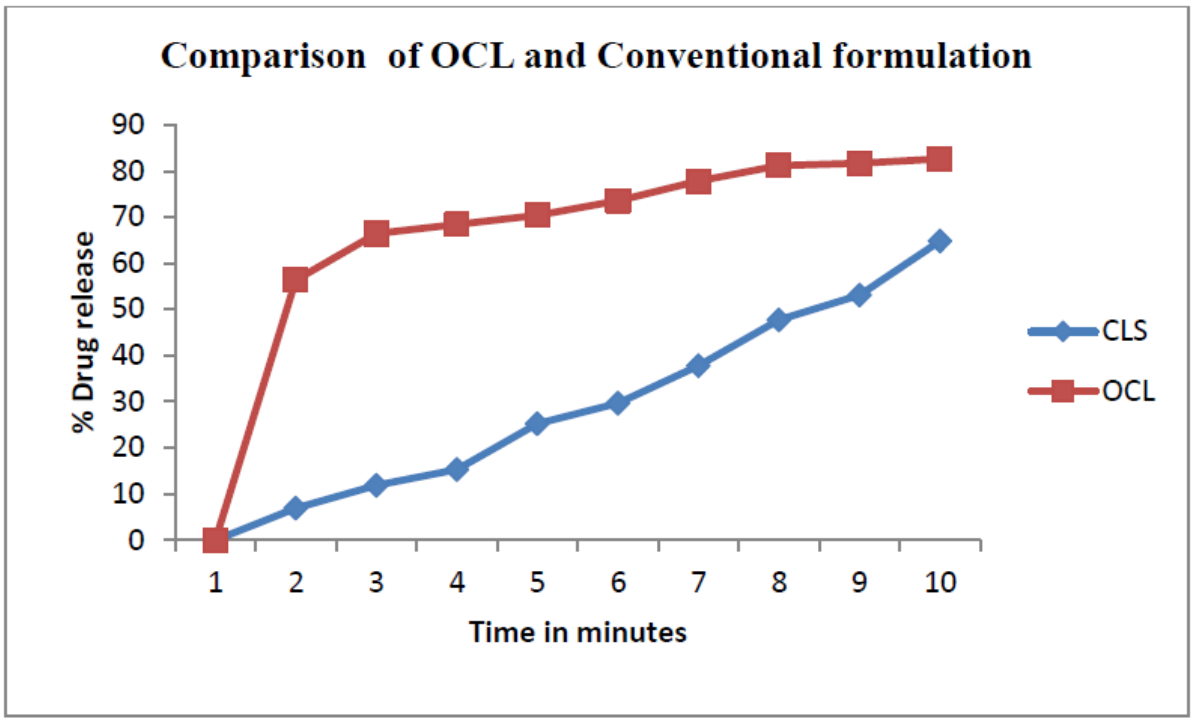

Fig. 5: *In-vitro* release profile comparison between OCL and conventional tablet

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