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Original Article

DESIGN AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS USING SINTERING TECHNIQUE

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ABSTRACT

Objective: Itopride Hydrochloride (ITO) is a prokinetic agent commonly used for the treatment of gastroesophageal reflux disease. It activates GI propulsive motility due to its dopamine D2 antagonizing activity and acetylcholinesterase inhibitory activity. The present work deals with application of sintering technique to matrix tablets of itopride hydrochloride to achieve sustained release using hydrophobic polymers

Methods: Eudragit L-100 and carnauba wax were used in combination to achieve sustained release. A 3^2 factorial design was used to study the effect of sintering and various ratios of Eudragit and carnauba wax on percent drug release at 10 h, contact angle, and porosity. The tablets were also evaluated in terms of tensile strength, *in-vitro* dissolution and pharmacokinetic studies.

Results: The results of a 3^2 full factorial design revealed that sintering caused decrease in drug release as compared to unsintered tablets. The concentration ratio of Eudragit L-100 and carnauba wax polymers also significantly affected the release profile. Carnauba wax maintained the integrity of the matrix, whereas Eudragit L-100 slowly eroded in the matrix as the drug was released. Thus, the area-to-volume ratio of the tablet remained constant over the duration of the drug release. The optimized formulation followed first order release kinetics with the diffusion-erosion mechanism. *In vivo* studies revealed higher T_{max} of matrix tablet compared to a plain drug which is suggestive of slower absorption. However, the $AUC_{0\text{-}10\,h}$ of the optimized formula and plain drug was found to be 1.561 h. µg/ml and 0.481 h. µg/ml respectively.

Conclusion: Matrix tablets of Itopride hydrochloride can be formulated using the sintering technique to achieve sustained drug release along with increased bioavailability.

Keywords: Sintering, Matrix tablets, Eudragit L-100, Carnauba wax.

INTRODUCTION

Oral route is one of the most convenient routes for drug administration among all the routes [nasal, ophthalmic, rectal, transdermal and parenteral routes] that have been explored for systemic delivery of drugs. Sustained release tablets are commonly taken only once or twice daily, compared with conventional forms that may have to be taken three or four times daily to achieve the equivalent therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or consistent blood level of a drug often translates into better patient compliance, as well as enhanced the clinical efficacy of the drug for its intended use [1, 2].

The sustained drug delivery can be achieved by matrix tablet wherein a solid drug is dispersed in an insoluble matrix. Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. The rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. The matrix tablets can be prepared by wet granulation method. Wet granulation method has several advantages over dry granulation method like better flow properties of granules and less generation of dust while mixing [1-5]. Thermal sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. It is a simple, effective and economical process to obtain sustained release of drug from the tablet with comparatively less quantity of polymer [6]. The sintering technique is used extensively for sustained release in various drug i.e. Propranolol hydrochloride, Diltiazem Hydrochloride and Ketorolac tromethamine [7-9].

ITO a BCS class III drug, it is freely soluble in water with Log p value of 2.32 and 60% bioavailability. ITO (50 mg) is given thrice a day along with proton pump inhibitors like omeprazole, esomeprazole, and pantoprazole. ITO is used for treatment of various digestive conditions like heartburn, regurgitation, epigastria pain, esophagitis etc. These conditions include GERD, non ulcer dyspepsia, chronic gastritis and a very important complication seen in diabetics where in the gastric emptying is markedly reduced i.e. diabetic gastro paresis. By developing the sustained release formulation of ITO, the frequency of drug administration can be reduced to once a day and one can achieve better therapeutic response [9-11]. Hydrophobic polymer matrix systems are extensively used because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. In present study Eudragit L-100 (EL-100) and carnauba wax (C. wax) were used as matrix polymers and sustained release tablets were prepared by combining matrixing and sintering techniques to modulate the release profile of the drug.

MATERIALS AND METHODS

Materials

Itopride Hydrochloride (ITO) was obtained as a gift sample from Ami Life Sciences Pvt. Ltd. Baroda Gujarat, India. Xanthan gum was obtained from Hi Media Laboratories Pvt. Ltd. Mumbai, Eudragit L-100 was obtained from Roehm Pharma Polymers, Carnauba wax was obtained from Vishal Chem Mumbai, Microcrystalline cellulose, Magnesium stearate and Talc was obtained from M/S Lobachemie ltd, Mumbai.

Preliminary studies

Matrix granules of ITO were prepared by wet granulation method. Various polymers such as EL-100, C. wax, Xanthan gum (XG) and microcrystalline cellulose (MCC) were investigated as singly and in combination in different ratios. Polyvinyl pyrrolidone (PVP) dissolved in hydroalcoholic solvent (70% v/v) was used as a binder to prepare granules, which were passed through sieve no. 16. The granules were dried at 50 °C for 4h. The dried granules were screened through sieve no. 16 and stored at ambient temperature

for further studies. The granules were mixed with of magnesium stearate and talc in require quantity and compressed using rotary tablet compression machine (12 stations, Mini press–II MT, Rimek, India), using 12.5 mm diameter flat punches. The tablets were placed on aluminum foil and subjected to thermal treatment at 60 °, 70 ° and 80 ° C for 1, 2 and 3 h in hot air oven (Biomedica lab ovens).

Drug-Excipients compatibility study

ITO alone and in mixture with other excipients was subjected to FTIR and DSC studies to check the possibility of any interaction with each other. One month compatibility study was done on physical mixture at 40 °C/75% RH. Binary mixtures of ITO and all excipients in 1:1 ratio were subjected to specified conditions, IR spectra of a physical mixture of ITO and excipients were recorded to study the interaction of drug and polymer after a month. FTIR spectrum of resultant product was taken and compared with the spectrum of ITO.

The Differential scanning calorimetric thermograms of the pure drug, polymer and drug and polymer physical mixtures were recorded using differential scanning calorimeter (DSC823e Mettler Toledo, Japan). Approximately 2 to 5 mg of each sample was heated in a closed pierced aluminum pan from 30 °to 300 °C at a heating rate of 10 °C/min under a stream of nitrogen at a flow rate of 50 ml/min [12].

Experimental design

The optimization of sustained release formulation of ITO was done by using Design expert software (Design Expert trial version 7.0.3). Based on the results of preliminary studies combination of EL-100 and C. wax were used for further optimization studies. A 3^2 full factorial design was used where independent variables were ratio of EL-100 and C. wax (X_1) as 1:1, 2:1 and 1:2 and sintering time of 1,2 and 3h at 80°C (X_2) at three levels. The responses selected were percentage release after 10 h (Y_1), contact angle (Y_2) and porosity (Y_3). All other formulation and processing variables were kept invariant throughout the study. So a total of 9 formulations (F1-F9) were prepared.

Evaluation of granules

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated [13, 14]. Tablets from all the formulations were evaluated for various properties like hardness (Monsanto hardness tester), thickness (Vernier caliper), Friability and weight variation, drug content [13, 14].

Evaluation of matrix tablets

Contact angle measurement

The contact angle (θ) between purified water and tablet surfaces was determined by placing a 10 µl of water on surface of tablet using micropipette. Photographs of the drop in contact with water were taken. The drop was photographed after 10 sec. It was carefully superimposed on tracing paper and the contact angle was measured. Amaranth red was added to the water to ensure proper visibility of the drop [7].

Porosity

The true density was determined by helium pycnometry (Pycno 30, Smart Instruments, Mumbai, India) at 25±2 °C/40±5% RH. This method measures the volume of gas (Helium) displaced by a known mass of tablet, and gives the true density of the material. The sample must be completely dried. The porosity, ε, of the tablets was calculated by Eq. 1,

$$\varepsilon = 1 - \frac{\rho c}{\rho t} \ldots\ldots\ldots \text{Eq. 1}$$

Where ρ_c is the density of the tablet calculated from the weight and volume of the resulting tablet. P_t is the true density of powder [15, 16].

Tablet Tensile Strength

The breaking force of the tablets was measured using a tablet hardness tester (Monsanto hardness tester). Tablet dimensions were measured using a digital caliper (Vernier caliper). Tensile strength was calculated using Eq. 2 to eliminate the undesirable effect of variable tablet thickness on measured breaking force.

$$\sigma = \frac{2F}{\pi dt} \ldots\ldots\ldots \text{Eq. 2}$$

Where σ is the tensile strength (MPa), F is the observed breaking force (N), d is the diameter (mm), and t is the thickness of the compact (mm) [15, 16].

***In vitro* dissolution test**

Dissolution studies were carried out in USP type II (paddle type) dissolution apparatus (TDT-08L, Electrolab) in 900 ml medium at 37±0.5˚C at a rotation speed of 50 rpm. The dissolution medium comprised of 750 ml of 0.1 N HCl for first 2 h followed by 150 ml of a 0.2 M solution of trisodium phosphate dodecahydrateto adjust the pH to 6.8 for next 10 h. The pH was adjusted with 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8±0.05. The drug release at different time intervals was measured by a UV-visible spectrophotometer (Lab india3000, India) at 247 nm (in 0.1N HCl) and 258 nm (in pH 6.8). The release studies were conducted in triplicate (6 tablets in each set) and the mean values were plotted versus time with standard deviation (SD) of less than 3, indicating the reproducibility of the results [17]. Kinetics of drug release from the sustained release matrix tablets was studied using DDsolver Disso 1 software and mathematical models such as zero-order, first-order, Higuchi, Hixon-crowell, Korsmeyer-peppas models were evaluated by the model-dependent (curve fitting) method.

***In-vivo* pharmacokinetic studies**

Male Wistar rats, weighing 230–330 g, were fasted for 24 h with free access to water. The rats were divided into three groups of six rats each, viz., first group served as negative control, second group was administered pure ITO solution and third group was administered optimized formulation. Tablets were given orally to rats in a dose equivalent to 5 mg/kg of drug [18]. The rats were anaesthetized with the help of ether, and the retro-orbital method was used to removal of blood samples. Blood samples were withdrawn from the retro-orbital vein at intervals of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 h and analyzed by bioanalytical HPTLC method using a mixture of n-butanol: toluene: ammonia (8.5:0.5:1 v/v) as mobile phase [19] and detected at λ_{max} of 258 nm [20]. A simple protein precipitation method was employed for extraction of the drug from rat plasma using 10% perchloric acid. The protocol for the animal experiment was approved by the Institutional Animal Ethical Committee (Ref no. AISSMS/IAEC/14-15/01-21).

Stability studies

The formulations were subjected to the accelerated stability studies (40° C±2° C/75%RH±5%RH). Samples were withdrawn periodically at 0, 15, 30 d and evaluated for drug content, weight of tablet and *in vitro* dissolution studies.

RESULTS AND DISCUSSION

Preliminary studies

From the dissolution study of all trial batches, it was evident that release from the matrix is largely dependent on the polymer, drug diffusion and matrix erosion. The drug release study was carried out up to 10 h. The percentage drug release from batch A1 (ITO: EL-100 1:1 ratio), A2 (ITO: C. wax 1:1 ratio), A3 (ITO: XG1:1 ratio) and A4 (ITO: MCC 1:1 ratio) was found to be 92.62(8 h), 91.87(8 h), 91.21(8 h) and 99.86 (4 h) % respectively. After carrying out sintering of same batches, drug release was found to be 76.45, 80.03, 83.55% in 10 h and 99.7% in 6 h respectively. Batches A5 (ITO: EL-100), A6 (ITO: C. wax), A7 (ITO: XG) with drug polymer ratio of 1:2, exhibited comparatively lesser amounts of drug release than A1, A2 and A3 of 98.01, 99.13 and 99.72% in 10 h respectively. This could be attributed to the fact that, large concentration of EL-100 polymer induces the formation of strong films resistant to gastric fluid that slowed down the rate of water diffusion into the tablet matrix. This may result in the retardation of drug release. This polymer after forming salts dissolves above pH 5.5 and disperses in water, forming latex [21].

There was no significant decrease in release drug values in batches A5, A6 and A7 despite using double the concentration of polymers than A1, A2 and A3 (1:1). Hence, a combination of both the polymers were selected in the third trial batch i.e. A8 and A9 with both the batches having drug and polymers ratio of 1:1. The batch A8 had polymers (EL-100: XG) in the ratio 2:1. Due to combination of a hydrophilic (XG) and hydrophobic polymer (EL-100) the release profiles of these batches changed accordingly. XG due to its tendency to swell in aqueous systems retarded the release profile [14]. The percentage drug release from batch A8 was 99.86 % in 10 h. After sintering drug release of 97.45 % was observed. This indicated that sintering did not result in a significant change in percent release. Since melting point of XG is high (270 °C), its effective sintering could not be carried out. Hence XG was not selected for further study. Therefore C. wax (melting point 80-86°C) was selected for A9 batch and further combinations were made of C. wax with EL-100. The batch A9 had polymers (EL-100, C. wax) in the ratio 2:1. The percentage drug release from batch A9 was found to be 92.48 % and after the sintering at 80 °C for 3h the percentage drug release was found to be 74.75%. Since a remarkable change in percent release was observed after sintering, combination of EL-100 and C. wax was investigated further.

Table 1: Preliminary batches of ITO matrix tablet

Formulation	ITO	EL100	C. wax	XG	MCC	PVP	Mg. stearate	Talc
A1	135	135	-	-	-	80	25	25
A2	135	-	135	-	-	80	25	25
A3	135	-	-	135	-	80	25	25
A4	135	-	-	-	135	80	25	25
A5	135	270	-	-	-	80	25	25
A6	135	-	270	-	-	80	25	25
A7	135	-	-	270	-	80	25	25
A8	135	90	-	45	-	80	25	25
A9	135	90	45	-	-	80	25	25

Drug excipients compatibility studies

The samples were checked for physical changes such as discoloration and odour no changes were observed during compatibility study.

Fourier–transform infrared spectroscopy

The IR absorbance spectrum of ITO was recorded using Fourier–transform infrared spectrometer (460 Plus, Jasco) over a range of 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}. The major drug peaks (functional group) at 3223, 3286 cm^{-1}[N-H asymmetric and symmetric structure respectively]; 1650 cm^{-1}[C=O bending]; 1509 cm^{-1}[C=C aromatic structure]; 2968, 2622 cm^{-1} [C-H structure of aromatic and C-H structure of CH_3 group respectively] were seen in subsequent spectra. The characteristic peaks of ITO were not altered and hence it was concluded that no any significant interaction between ITO and selected excipients was evident. Insignificant shifting of spectra or reduction in peak intensity was evident.

Differential scanning calorimetry

The thermogram of ITO shows a sharp melting endotherm at 194.71°C (fig. 1). The thermogram of a binary mixture of ITO with C. wax showed two endothermic peaks corresponding to the melting point of C. wax at 83.58 °C and of the drug. Similarly the drug endotherm was evident in thermogram of its binary mixture with EL-100. These thermograms indicate that drug and polymers were compatible with each other and also point to the fact that drug is not molecularly dispersed in the polymer matrix.

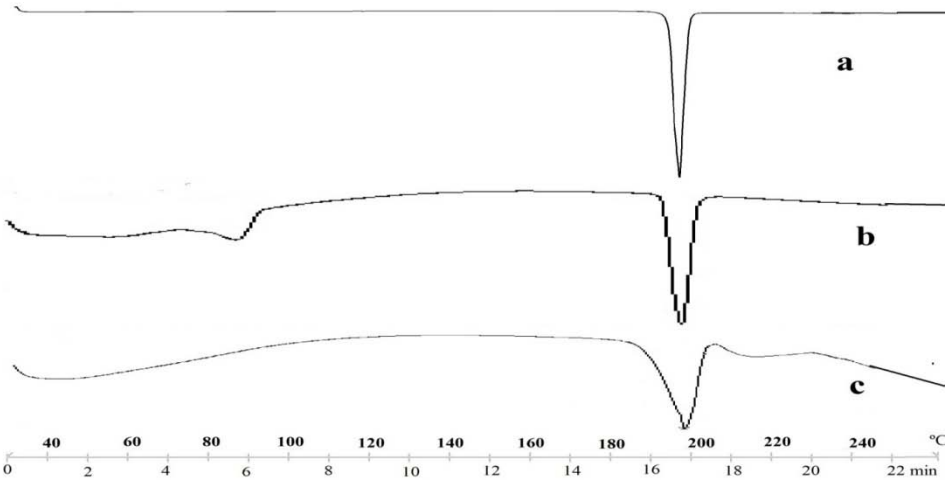

Fig. 1: DSC thermogram of drug excipients compatibility studies a) Pure drug b) drug+C. wax c) drug+EL-100

Evaluation of granules and matrix tablets

Various batches given by study design were evaluated. The granules prepared for compression of matrix tablets were evaluated for their flow properties. The bulk density was within the range of 0.411 to 0.453 gm/cm^3. Tapped density ranged between 0.502-0.598 gm/cm^3. This indicates good packing capacity of granules. Angle of repose was within the range of 22.98 to 25.12 i.e. granules were of good flow properties. Compressibility index was found to be 13.21-24.05 showing good flow characteristics. Hausner ratio ranged from 1.152-1.454 which confirmed above findings [15]. All the tablets showed elegant appearance. The hardness of the tablets of all formulations was within the range of 5.03 to 5.7 kg/cm^2, indicating satisfactory mechanical strength. The particle loss in the friability test was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablets [18]. The variation in

weight was within the range of±7.5% complying with Pharma-copoeia specifications [18]. The percentage of ITO in all formulations was in the range OF 97.92-99.46% indicating content uniformity was within the limits (±10%).

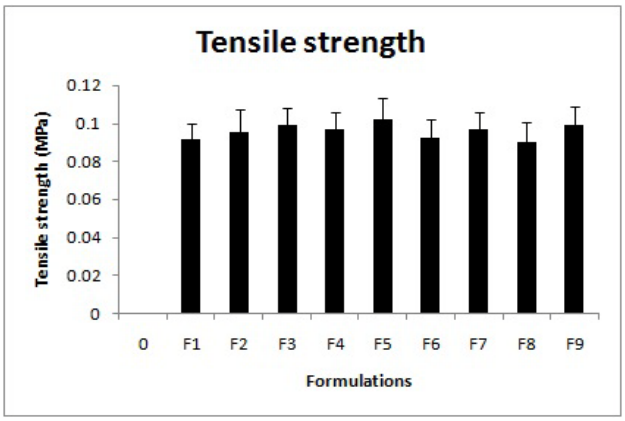

Fig. 2: Tensile strength for matrix tablets of batches F1-F9

Tensile strength

Tensile strength can be used as a measure of the inherent strength of compacted material and the ability of particle binding. The tensile strength of all tablet formulations was within the range of 0.0902 to 0.1022 MPa (fig. 2) indicating satisfactory mechanical strength.

Sintering caused increased binding of particles in matrix tablets, which resulted in increased tortuosity and decreases porosity. An increase in tensile strength resulted in decreased drug release rate. The tensile strength was found to increase with increasing in polymer concentration ratio [22, 23].

Factorial design

A 3^2 factorial design was applied to study the effect of sintering (X_2) on the drug release from matrix tablet of ITO with different ratios of EL-100 and C. wax (X_1). The dependent variables chosen were amount of drug release after 10 h ($\%_{rel10\ h}$), contact angle (°) and porosity (table 2). A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. Analysis of experimental results was carried out by using Design Expert V 9.1 software. Quadratic model was suggested to run the design. F-values, P-value and model F-value for percent drug release at 10 h, contact angle and porosity were obtained from ANOVA. The selection of model and polynomial equations are listed in (table 3).

Table 2: Reponses of batches in 3^2 factorial designs

Batch code	Coded value		$\%_{rel10\ h}$	Contact angle (°)	Porosity
	X_1	X_2			
F1	1:2 (-1)	1h (-1)	91.41	43	0.1507
F2	1:2 (-1)	2h (0)	88.38	53	0.1424
F3	1:2 (-1)	3h (+1)	81.79	64	0.1628
F4	1:1 (0)	1h (-1)	91.48	50	0.1652
F5	1:1 (0)	2h (0)	86.65	58	0.1288
F6	1:1 (0)	3h (+1)	78.78	66	0.1452
F7	2:1 (+1)	1h (-1)	91.63	55	0.1916
F8	2:1 (+1)	2h (0)	85.53	61	0.1500
F9	2:1 (+1)	3h (+1)	75.77	67	0.1479

Table 3: Summary of results of regression analysis

Model	$\%_{rel10\ h}$		Contact angle		Porosity	
	coefficient	p-value	coefficient	p-value	coefficient	p-value
Intercept	86.82	0.0001	57.89	0.0001	0.23084	0.0105
X_1	-1.37	0.0003	3.83	0.0001	-2.01101	0.0486
X_2	-6.30	0.0001	8.17	0.0001	-0.047408	0.0159
X_1X_2	-1.66	0.0003	-2.25	0.0004	-8.37084	0.0072
X_1^2	0.046	0.7217	-0.83	0.0190	4.0208	0.0341
X_2^2	-1.78	0.0006	0.17	0.4228	0.020167	0.0068
R^2	0.9997		0.9996		0.9784	

***In vitro* dissolution study**

From the dissolution study of batches F1 to F9, it can be concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 10 h. The percentage drug release from batch F1 to F9 ranged from 75.77 to 91.63%. The tablets containing a higher concentration of EL-100 and lower concentration of C. wax showing retardation in drug release. The concentration of EL-100 increased from F1 to F9 batches whereas C. wax decreased. C. wax is partially soluble at all pHs [24, 25] whereas EL-100 undergoes dissolution in pH range of above 5.5 [26]. This causes slow erosion of the polymer matrix providing micro channels through which the drug diffuses out. Additionally sintering causes the wax to melt, redistribute and coat drug and excipients particles, thus causing retardation of drug release [27]. The drug release from these polymer-wax matrices is described by a combination diffusion/erosion mechanism [28]. Dissolution profiles for all batches were shown in (fig. 3).

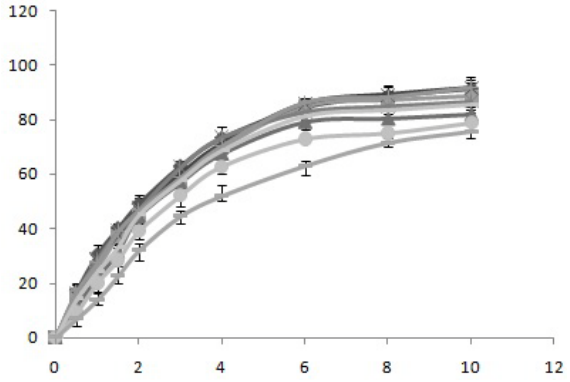

Fig. 3: *In vitro* drug release profiles for matrix tablets of batches F1-F9

The drug release kinetics ware determined by DD solver disso 1 software. The first order model was best fitted for all nine formulations as it showed maximum R^2 value. The values were in range of 0.9719 to 0.9966.

Statistical analysis of percent drug release at 10 h (Y_1) the Model F-value of 1901.08 implied that the model was significant. P value was found to be 0.0001, which indicated that model terms were significant. The coefficients of the variable terms in the polynomial equation for response Y_1 (Eq.3) indicated that sintering time, which was inversely related to drug release at 10 h had a more prominent effect than polymer concentration.

$$\%_{rel\ 10\ h} = +86.82 - 1.37X_1 - 6.30X_2 - 1.66X_1X_2 + 0.046X_1^2 - 1.78X_2^2. \quad (R^2 = 0.9997)\ \text{Eq. 3}$$

Response surface plot of drug release at 10 h, the relationship between the variables at different levels and response was further elucidated by constructing 3-D response surface plots. The effects of X_1 and X_2 on response variables are shown in (fig. 4). Increase in EL-100 and decrease in C. wax resulted in retardation of drug release. Similar effect was obtained with sintering time.

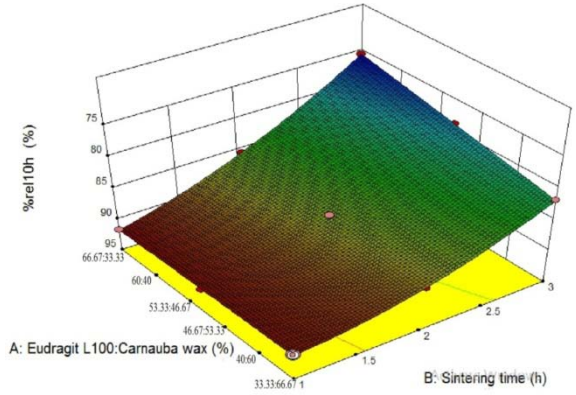

Fig. 4: Response surface plot for %rel10 h

Contact angle

The effect of sintering on the wettability of the tablet surfaces was established by taking the photographs of the tablet. On the tablet surface, drop of purified water containing amaranth red was placed to measure contact angle. The contact angle of sintered tablet was greater than that of unsintered tablet, as shown in fig. 5. This clearly indicated that sintering decreases the wettability of tablet surfaces. The contact angle from batch F1 to F9 ranged from 43 to 67 (table 2).

Fig. 5: Photo images showing contact angle of water with a) unsintered tablet and b) sintered tablet of F9 batch

The wettability of tablet surface can be indicated by contact angle. It is an important physical property that profoundly impacts the release of the drug especially from a hydrophobic matrix. The surface of the tablets made from wet granulation consists of a heterogeneous mixture of the ingredients of the tablet. After sintering, the hydrophobic polymer can be considered to be more uniformly dispersed on tablet surface. It led to an increase in the contact angle of the tablet surface which was evidenced by the higher contact angle and lower wettability [7]. When tablets were exposed to temperatures over the melting point of the incorporated polymer, the polymer present in liquid state will move through the matrix of the tablet and get filled between the pores of the matrix without affecting the overall shape of the tablet. This coating of the drug particles is generally referred to as in situ micro-coating [27].

Statistical analysis of contact angle (Y_2) the F-value of 1573.80 and P value was found to be 0.0001, which indicated that the quadratic model was significant.

The polynomial equation (4) for response Y_2 (contact angle) showed that sintering time had a more pronounce effect on contact angle than polymer concentration. The negative and low coefficients of the interaction term (X_1 and X_2) indicated an insignificant.

$$\text{Contact angle} = +57.89 + 3.83X1 + 8.17X2 - 2.25X1X2 - 0.83X12 + 0.17X22.\ (R2 = 0.9996).\ \text{Eq. 4}$$

Response surface plot of contact angle, the relationship between the variables at different levels and response was further elucidated by constructing 3-D response surface plots. The effects of X_1 and X_2 on response variables were shown in (fig. 6). An increase in contact angle with increase in X1 and X_2 factors was observed.

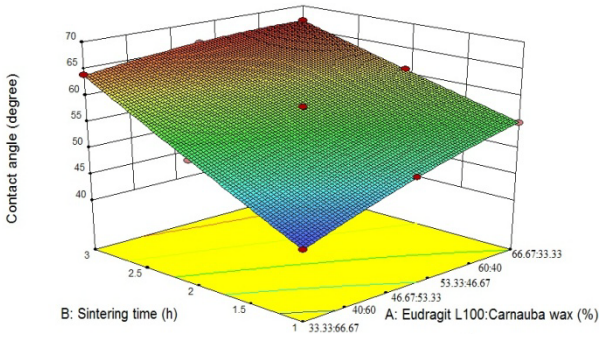

Fig. 6: Response surface plot for contact angle

Porosity

Tablet porosity is regarded as a measure of the tableting process. Variations in tablet porosity reflect various aspects of tablet compression performance. It is also related to tablet disintegration and dissolution [29]. The porosity of all batches was in the range of 0.1288 to 0.1916. The rate of drug release was found to be inversely related to sintering time of matrix structure. Such increase in sintering time results in a decreased drug release rate because sintering is affected by porosity and mechanical strength of matrix tablet. Sintering time causes a increased tortuosity of the path of the drug [30]. The porosity of all batches F1-F9 as shown in (table no. 2.)

Statistical analysis of porosity (Y_3), The F-value 27.19 implies that the model was significant. P value was found to be 0.0106, which indicated that the quadratic model terms are significant. The negative and high value of coefficient of factor X_1 (polymer concentration) in the polynomial equation 5 for response Y_3 (porosity) is indicative of a dominant role of both polymers in the particle rearrangement process during sintering. Though sintering time itself did not play a defining role in this response as evident from the low coefficient for X_2, the high coefficient for the term X_1X_2 portends a strong interaction between the two independent variables. The melting point of C. wax is reported to be between 78-88° C [31] whereas of EL-100, it is>130° C [32]. Thus we understand that the sintering temperature of 80° C causes complete fusion of C. wax and EL-100 may just soften at this temperature. The densification of the matrix structure may be brought about by the action of capillary pressure caused by collapse of melt bridges between particles and by rearrangement of particles sliding over each other [33].

$$\text{Porosity} = +0.2308 - 2.011X1 - 0.047X2 - 8.37X1X2 + 4.02\ X12 + 0.020X22.\ (R2 = 0.9784)\ \text{Eq. 5}$$

Response surface plot of porosity, the relationship between the variables at different levels and response was further elucidated by constructing 3-D response surface plots. The effects of X_1 and X_2 on response variables were shown in (fig. 7). A decreases porosity with increase in X_1 and X_2 factors.

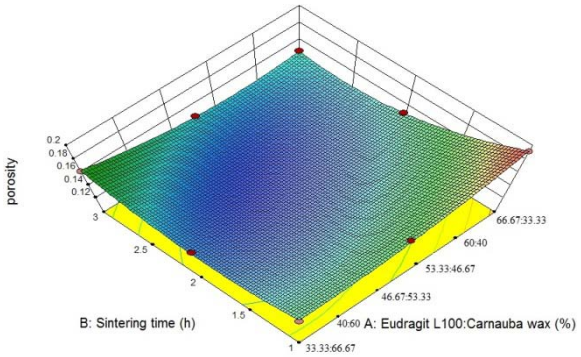

Fig. 7: Response surface plot for porosity

Validation of optimizedmodel

Validation of optimized model based on acceptance criteria and desirability factor Design Expert V 9.1 software suggested three optimum formulations of which one was selected based on the desirability values. The optimized formulation had polymer composition of 2:1 of EL-100 and C. wax with sintering time of 3h. The optimized formulation which was further subjected to *in vivo* studies. The experimental values of the responses matched the predicted values with a percent error in the range of 0.54-0.98.

In vivo pharmacokinetic study

In vivo pharmacokinetic study was performed in Wistar rats. Various pharmacokinetic parameters like C_{max} (maximum concentration) and T_{max} (time to reach maximum concentration) were directly obtained from the plasma concentration time curve (fig. 8). T_{max} for matrix tablets and pure drug was found to be 8h and 1h with C_{max} 0.209µg/ml and 0.172µg/ml, respectively. The elimination constant (K_{el}) for drug in the matrix tablet was found to be 0.096/h while for the pure drug it was found to be 0.469/h. Based on the elimination constant, the biological half life was computed and was found to be 7.16 h for the matrix tablet and 1.47 h for the pure drug. An increase of about 4.8 times was evident in the half life of drug in matrix tablet in comparison to the pure drug points to the increased residence time of drug in biological system. The $AUC_{0\text{-}10\ h}$ of optimized tablet and plain drug was found to be 1.561 h. µg/ml and 0.481 h. µg/ml respectively. After oral administration, ITO undergoes rapid and extensive absorption, reaching peak plasma concentration in less than an hour and is eliminated via kidneys with an elimination half life of 6 h [34]. The sintered matrix tablets displayed a remarkable increase in bioavailability due to prolonged plasma residence as evident from the pharmacokinetic parameters. Thus we may conclude that effectively the dosing frequency can be reduced.

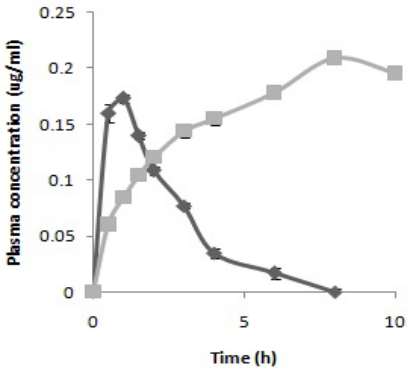

Fig. 8: *In vivo* drug release profile of optimum formulation and pure drug ITO of matrix tablets

Stability study

Stability studies of optimum formulation revealed no significant changes in the physical parameters when stored at temperature and humidity conditions of 40°C/75% RH and at room temperature. No significant reduction in the content of the active drug was observed over a period of one month.

CONCLUSION

The present study involved prepared of sustained release matrix tablets of ITO using hydrophobic polymers and study of sintering technique in modulating drug release. Carnauba wax and Eudragit L 100 were used as release retarding polymers. A 3^2optimization design was applied so as to achieve tablets with optimum drug release. Drug release mechanism was found to be diffusion-erosion because of polymer-wax combination. Optimization batches were studied for porosity, contact angle and tensile strength so as to understand effect of sintering on abovementioned properties. Decreased wettability and porosity along with increase in contact angle was evident for sintered tablets. These changes induced retardation in drug release. *In vivo* studies of optimized batch revealed 4.8 times increase in $t_{1/2}$ and sustained release of drug upto 10 h.

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CONFLICT OF INTERESTS

Declare none

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