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Process variable studies for the preparation of optimized drug delivery system using central composite design

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ABSTRACT

This research work aimed to study process variable studies for the tasteless drug resin complex of Propranolol hydrochloride and Kyron-T 314. The effect of different parameters such as swelling time, stirring time, pH, Temperature, drug resin ratio, as well as resin activation, was optimized by taste and percentage of drug loading. The formulation DRC (Drug Resin Complex) was characterized by Infrared Spectroscopy. Differential Scanning Colorimetry, and X-ray Diffraction Pattern. Tablets were formulated by the Direct Compression method with Hydroxypropyl methylcellulose (HPMC) as a binder. Sodium Starch Glycolate (SSG) and Kyron-T 314 as a super disintegration, In these batches, optimum hardness was achieved but disintegration time was found to be 30 Seconds, so further trials were planned by using different super disintegrants such as Sodium starch glycolate and Kyron-T 314 by direct compression method. Tablets formulated with 10% Kyron-T 314 showed comparatively low disintegration time (30 Sec), wetting time (26 Sec), and Friability (0.7%) than the other batches. In the present study, we optimized the conditions require for maximum drug loading of Propranolol hydrochloride and Kyron-T 314. Among different super disintegrants, Kyron-T 314 was found suitable with the Drug resin complex to get the low disintegration time, wetting time, and friability of tablets. Hence, optimized DRC batches were formulated by proper balancing of the concentration of independent variables to attain desired dependent response using 32 CCD. Thus, 32 CCD is an efficient tool in optimization experiments.

Keywords: Ion exchange resin; Central composite design; Drug resin complex; Propranolol hydrochloride; Kyron T-314

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INTRODUCTION

"Worst the taste of the medication, the better the cure" was once the prevailing attitude. Today this trend has changed and great importance is given to pharmaceutical products' organoleptic characteristics, i.e., appearance, odor, and taste. Masking a drug's unpleasant taste improves the patient's compliance and product value.

More than 50% of pharmaceutical products are administered orally for several reasons, of which better patient compliance and the existence of highly developed technology are most important. Oral administration of a drug having a bitter and obnoxious taste with an acceptable level of palatability is a challenge to the pharmacist in the present world, especially in pediatric and geriatric formulations. Thus, taste masking has become a potential tool in the present-day pharmaceutical industry to improve patient compliance and the product's commercial success [1].

Ion-exchange resins (IERs) are high-density polymer molecules with active cationic and anionic groups attached to a water-soluble polymer core. These groups have the ability to exchange ion counters charged in reverse, thus absorbing ions in the polymer matrix. Since many drugs have ionic properties in their molecule, resin charging provides a way for weak ionic accumulation so that the dissociation of the drug-resin complex does not occur under the pH conditions of the saliva, thus causing the taste to hide. For the purpose of masking the taste of weak cation or weak anion exchange resins are used, depending on the type of drug [2].

The advantage of ion-exchange materials for taste masking is their ability to bind and exchange charged drug molecules. In general, for taste masking purposes weak cation exchange or weak anion exchange resins are used, depending on the nature of the drug. Sometimes strong cation exchange resins are also used for taste masking purposes. The nature of the drug-resin complex formed is such that the average pH of 6.7 and cation concentration of about 40 meq/L in the saliva is not able to break the drug-resin complex but it is weak enough to be broken down in the acidic environment of the stomach.

The batch process is usually the preferred method due to its ease of operation. This process involves slurring the drug and resin in water, filtering or decanting the liquid on the top, slurring the resin with the desired acid, base, or salt solution to change the cycle (if necessary), decanting and washing with water several times, and treating with the appropriate drug solution. After complexation, the complex formed is washed with water and dried [3].

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was obtained from Liberates Chemicals Surat Gujarat. Polacrilin potassium (Kyron T-314) was gifted by Coral Pharmaceutical Pvt. Ltd. Ahmadabad. Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Starch Glycolate (SSG), Saccharine, Talc, Magnesium stearate, and Mannitol have been purchased from sigma laboratories Pvt. Ltd. Mumbai. Microcrystalline cellulose (MCC) (Avicel pH 101) from Gujarat Micro wax Pvt. Ltd. Ahmedabad India. All the chemicals and solvents used were of analytical grade.

Methods

Formulation of a drug resin complex Formulation of DRC was done by the batch process; IER Kyron T 314 (100mg) was placed in a beaker containing deionized water (25mL) and allowed to swell for a definite period. An accurately weighed amount of Propranolol hydrochloride (Drug: IER – 1: 3) was added and stirred for the desired period. The mixture was filtered and the residue was washed with deionized water. The filtrate was analyzed by U.V. spectrophotometer (UV-1800) Shimadzu, for the unbound drug at 228 nm and percentage drug loading was calculated.

Experimental design A 3^2 CCD was adopted for the optimization study. Two independent variables investigated were functional excipients such as a Binder ((HPMC, X1) and super-disintegrant (Kyron T-314, X2) and Sodium starch glycolate. The effects of these independent variables are Swelling time, stirring time, pH, temperature, and resin activation. Polynomial equations are generated and used to express the function of independent variables (HPMC and Kyron T-314) Y = b0 + b1 X1 + b2 X2 + b3 X1 X2 + b4 X1 2 + b5 X2 2 + b6 X1 X2 2 + b7 X1 2 X2 …… (1) Where Y is the dependent variable, b0 is the arithmetic mean response of the thirteen runs. The main independent variables, that is, effects X1 and X2 represent the average result of changing one factor at a time from its lower values to its higher values. 3 2 CCD is most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. In the present study, 3 2 CCD was considered to be better as the values of the response surfaces were not known from the previous findings. Hence, 3 2 CCD was chosen for the optimization of all variables. The responses were analyzed using Design Expert® 13, Version 13.0.5.0 64-bit (trial version) shown in (**Tab. 1 & 2.**) [4].

Evaluation of complex

a. **Taste of drug-resin complex** Taste masking of Propranolol Hcl was carried out on 2 healthy human volunteers. The first pure drug was given to the volunteers and taste was noted. After the administration of water and after rinsing the mouth, the complex was given to the volunteer. The taste difference between pure drugs and the complex was noted and compared.

b. **Drug content and % drug loading:** A dose equivalent to 5 mg of drug-resin complex dissolves in 900 ml 0.1N HCl. Absorbance was measured using a Shimadzu UV-1800 spectrophotometer at 228 nm. The absorbance value was put in Beer's Lambert's

Tab. 1. Central composite layout Optimization of swelling and stirring time.

Batch No.	Swelling Time	Coded Value	Stirring Time	Coded Value
DRC 1	20	-1	30	-1
DRC 2	40	0	30	-1
DRC 3	60	1	30	-1
DRC 4	40	0	60	0
DRC 5	60	1	60	0
DRC 6	20	-1	60	0
DRC 7	60	1	120	1
DRC 8	20	-1	120	1
DRC 9	40	0	120	1
DRC 10	40	0	60	0
DRC 11	40	0	60	0
DRC 12	40	0	60	0
DRC 13	40	0	60	0

Tab. 2. Central composite layout optimization of temperature and pH.

Batch No.	Temperature	Coded Value	pH	Coded Value
DR 1	30	-1	1.2	-1
DR 2	40	0	1.2	-1
DR 3	50	1	1.2	-1
DR 4	40	0	7	0
DR 5	50	1	7	0
DR 6	30	-1	7	0
DR 7	50	1	8	1
DR 8	30	-1	8	1
DR 9	40	0	8	1
DR 10	40	0	7	0
DR 11	40	0	7	0
DR 12	40	0	7	0
DR 13	40	0	7	0

Equation and measured the drug content. Suppose the drug content measured by Beer's Lamberts Equation was 4.7 mg. 5 mg contains % drug loading So, 4.7 mg contains =? =94 % Drug loading by this formula drug content and %, drug loading was measured.

c. **Optimization of swelling and stirring time:** Optimization of swelling and stirring time was done by changing swelling time as well as stirring time. For different batches, Kyron T 314 (200 mg) was soaked in 250 mL of deionized water in a beaker for 20, 40, and 60 min respectively. The complexation by the batch process adopted for the formation of DRC by stirring for 30 and 120 min for different batches and percentage drug loading and taste were determined.

d. **Optimization of temperature and pH on complex formation:** The complexation of 50 mg of drug with 300mg of resin, slurred in 25 mL of deionized water in a beaker, was performed at 250°C, 400°C, 600°C, and 800°C using temperature-controlled magnetic stirring for 30 min. The volume of the filtrate was made up to 50 mL with aqueous washing of DRC. The amount of bound drug was estimated spectrophotometrically (228 nm) from the unbound drug in the filtrate. Accurately weighed 50 mg of drug powder was added to 300 mg of resin slurred in 25 mL of different pH (1.2, 7, and 8) solution prepared from a standard solution of HCl and NaOH in a 100 mL beaker and maintained at 250 C. The drug loading efficiency was estimated.

e. **Optimization of resin activation:** Accurately weighed resin (25 mg), was placed on a filter paper in a funnel and then it was washed with double distilled water and subsequently with 1 N HCl (100 mL) for acid activation. The resin was rewashed with water until neutral pH was reached. Similarly, alkali activation of resin was performed, by replacing 1 N HCl with 1N KOH. For Acid- alkali activation, the resin was treated with 1 N HCl and 1N KOH (1 N HCl: 1N KOH = 50:50). This activated resin was used for the complexation process. The drug resin ratio, swelling, time, and stirring time were kept constant for the DRC formulation by batch process and percentage drug loading was determined.

Preparation of tablets: Three batches of the tablet (F1 to F3) were prepared with the help of Binder and Super-disintegrants (Hydroxy Propyl Methyl Cellulose (HPMC), Kyron T-314), and Three batches of the tablet (F4 to F6) were prepared with the help of binder HPMC, SSG. By (punch size–10 mm) direct compression method, Each binder and super-disintegrant are used in different concentrations respectively (**Tab. 3.**).

Formulation of a mouth-dissolving tablet: First of all, formulation of Oral Dispersible Tablets was done by direct compression technique for batch F1 to F6 by taking DRC equivalent to 10 mg of Propranolol HCl. MCC is used as the diluent, Hydroxy Propyl Methyl Cellulose and sodium starch glycolate are used as a binder, Kyron- T 314 as super-disintegrants, saccharine as a sweetener, mannitol as a soothing agent, talc as an anti-adherent, and magnesium stearate as a lubricant. All the ingredients were accurately weighed and passed through a 100 # sieve and mixed with complex. The above powder blend was compressed using a single-punch tablet machine [5].

RESULT AND DISCUSSION

Experimental design (Tab. 4.)

Data analysis: Statistically analyzed data indicated that the Swelling and Stirring Time values are heavily dependent upon the selected independent variables. Equations, release the response of Swelling and Stirring Time as ANOVA responses for various dependent variables are like:

Swelling Time = $59.39 + 3.66A + 7.57B - 0.58AB + 2.06A^2 + 0.28B^2 + 0.74A^2B - 0.63AB^2 + 0.38A^2B^2$ ….. (1)

Stirring Time = $59.34 + 3.23A + 8.07B - 0.58AB + 2.25A^2 + 0.46B^2$ ……. (2)

Response surface analysis: It was observed that Swelling and Stirring Time were depending on drug loading. There was a % drug loading increase in the level of both factors (**Fig. 1A**) and in the (**Fig. 1A**) Swelling and stirring time also increases the % drug loading (**Tab. 5.**).

Data analysis: Statistically analyzed data indicated that the pH and Temperature values are heavily dependent upon the selected independent variables. Equations, release the response of pH and Temperature as ANOVA responses for various dependent variables are like:

pH = $73.77 + 1.97A + 3.59B - 0.49AB + 1.33A^2 - 0.44B^2 + 0.58A^2B + 0.27AB^2 - 0.86A^2B^2$ …….. (1)

Temperature = $73.89 + 2.15A + 3.98B - 0.49AB + 0.90A^2 - 0.86B^2$ …… (2)

Response surface analysis: It was observed that pH and Temperature were depending on drug loading. There was

Tab. 3. Composition of propranolol hydrochloride mouth dissolving tablet.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
DRC (equivalent to 10 mg Propranolol HCl)	45	45	45	45	45	45
Mannitol	20	17.5	15	20	17.5	15
HPMC	7.5	7.5	7.5	7.5	7.5	7.5
Kyron- T 314	5	7.5	10	-	-	-
SSG	-	-	-	5	7.5	10
MCC (Avicel pH 101)	58	58	58	58	58	58
Saccharine	10	10	10	10	10	10
Talc	3	3	3	3	3	3
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Flavour (Vanilla)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total Weight	150	150	150	150	150	150

an % drug loading increase in the level of both factors and in the (**Fig. 2A**) pH and Temperature also increase the % drug loading.

Resin activation: The percentage of drug loading was also determined acid-treated resin, alkali-treated, and resin treated with both acid and alkali was found to be 61.4% ±1.31%, 45.80% ±0.26%, and 28.69% ±0.91% wt/wt respect the highest of percentage drug loading was acid-activated activated resin no major effect was found on percentage drug loading. Thus, further trials were made with inactivated resin (**Tab. 6.**).

Differential scanning colorimetry (DSC) study: By DSC curves, the thermal behavior of pure drug Propranolol Hydrochloride shows peak endotherm at 166.02°C (onset at 163.03°C and end set 167.62°C). The thermal the behavior of drug resin complex shows peak endotherm at 166.02°C (onset at 163.03°C and end set 167.62°C) (**Fig. 3A & B**).

X-Ray diffraction curves: The X-ray diffractogram of propranolol HCl confirms its crystalline nature, as evidenced by the number of sharp and intense peaks. The diffractogram resin (Kyron T314) showed diffused peaks, indicating its amorphous nature. However, the diffraction pattern of the drug resin complex represents the complete disappearance of crystalline peaks of drugs, whereas, the intensity of characteristic peaks of the pure drug was reduced and peaks were found to be broadened. These findings suggest the formation of a new solid phase with a lower degree of crystallinity due to complexation (**Fig. 4A & B) and** (**Tab. 7**).

Tab. 4. Optimization of stirring and swelling time.

Batch	Swelling Time	Coded Value	Stirring Time	Coded Value	% Drug Loading
	(A)		(B)		
F1	20	-1	30	-1	50.2
F2	40	0	30	-1	52.1
F3	60	1	30	-1	57.41
F4	40	0	60	0	59.8
F5	60	1	60	0	65.11
F6	20	-1	60	0	57.8
F7	60	1	120	1	72.88
F8	20	-1	120	1	68
F9	40	0	120	1	67.25
F10	40	0	60	0	59.1
F11	40	0	60	0	59.9
F12	40	0	60	0	58.98
F13	40	0	60	0	59.18

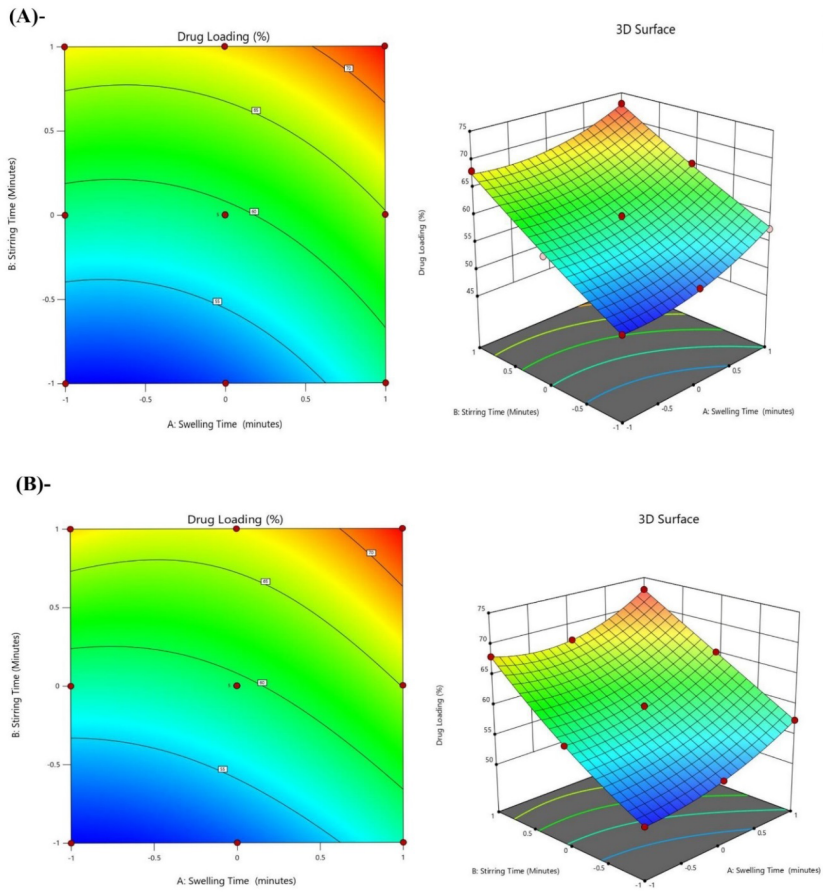
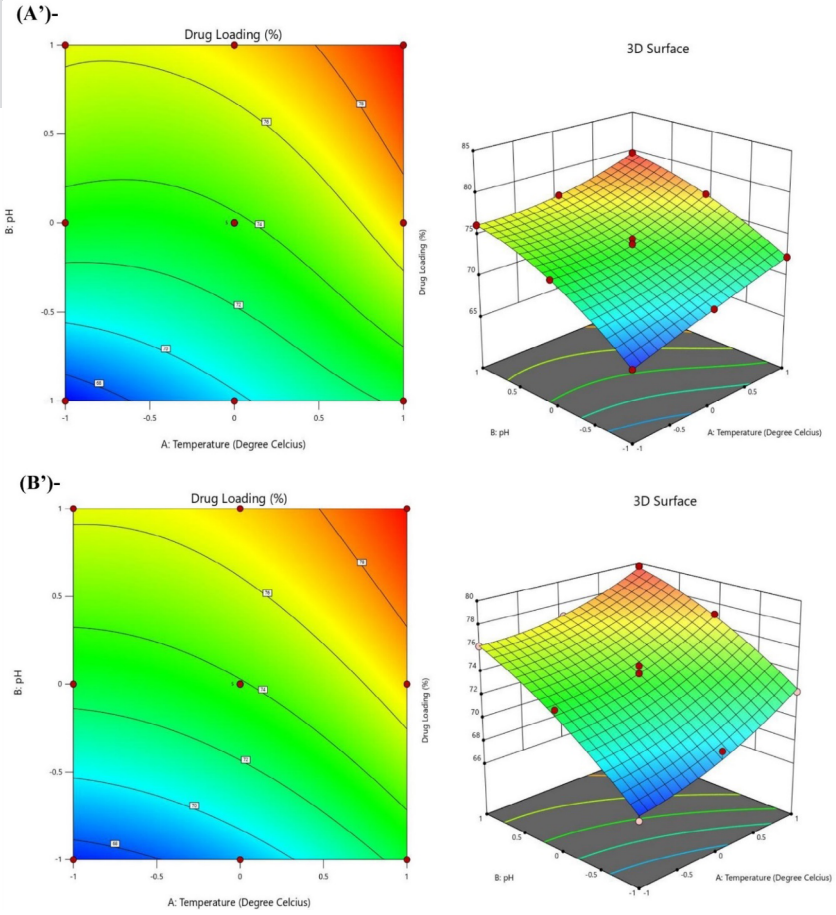


Fig. 1. Response surface and counter plot for–(A) Swelling Time, (B) Stirring Time, showing the influence of concentration of independent variables.

Tab. 5. Optimization of temperature and pH.

Batch	Temperature (A')	Coded Value	pH (B')	Coded Value	% Drug Loading
F1	30	-1	1.2	-1	66.87
F2	40	0	1.2	-1	69.73
F3	50	1	1.2	-1	72.34
F4	40	0	7	0	74.56
F5	50	1	7	0	77.07
F6	30	-1	7	0	73.12
F7	50	1	8	1	79.72
F8	30	-1	8	1	76.21
F9	40	0	8	1	76.92
F10	40	0	7	0	73.1
F11	40	0	7	0	73.89
F12	40	0	7	0	73.36
F13	40	0	7	0	73.92

Fig. 2. Response surface and counter plot for–(A') pH, (B') Temperature, showing the influence of concentration of independent variables.



Tab. 6. Effect of resin activation.

Batch	Drug: Resin ratio	Resin Activation	Swelling Time (Min)	Stirring Time (Min)	Temperature	pH	% Drug Loading
1	01:01	Acid activated	60	120	50	8	61.4
2	01:03	Acid activated	60	120	50	8	60.09
3	01:05	Acid activated	60	120	50	8	61.1
4	01:01	Alkali activated	60	120	50	8	45.8
5	01:03	Alkali activated	60	120	50	8	45.56
6	01:05	Alkali activated	60	120	50	8	45.24
7	01:01	Acid-Alkali Activated	60	120	50	8	28.69
8	01:03	Acid-Alkali Activated	60	120	50	8	27.78
9	01:05	Acid-Alkali Activated	60	120	50	8	28.18

Evaluation of the tablet

A. **Uniformity of thickness:** The uniformity of thickness was measured using a Vernier calliper the results are depicted in table 8. Tablet thickness should be controlled within a ±5% variation of a standard value.

B. **Hardness:** The hardness of the tablet from each

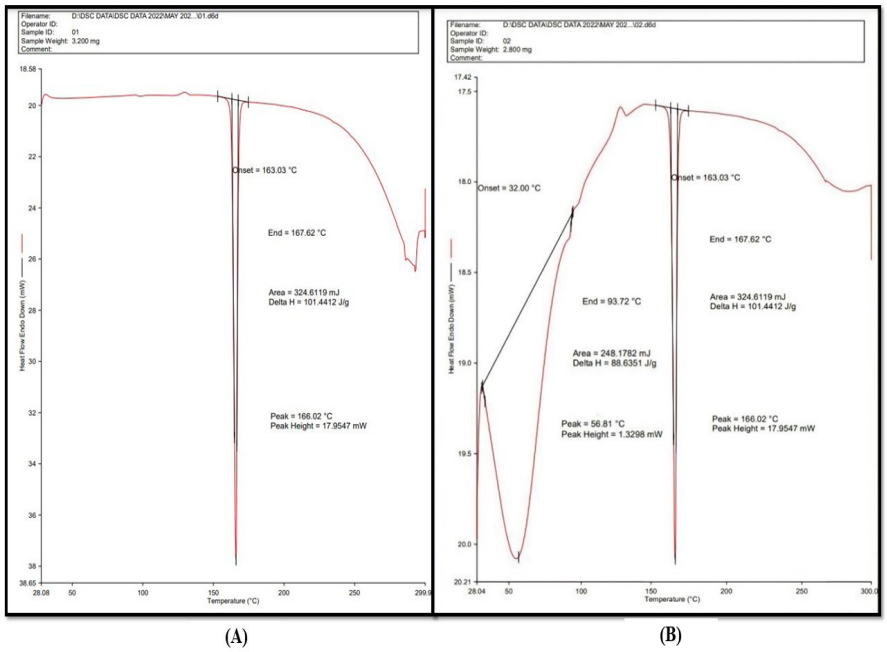


Fig. 3. (A) DSC of Drug (Propranolol Hydrochloride) (B) DSC of a drug resin complex

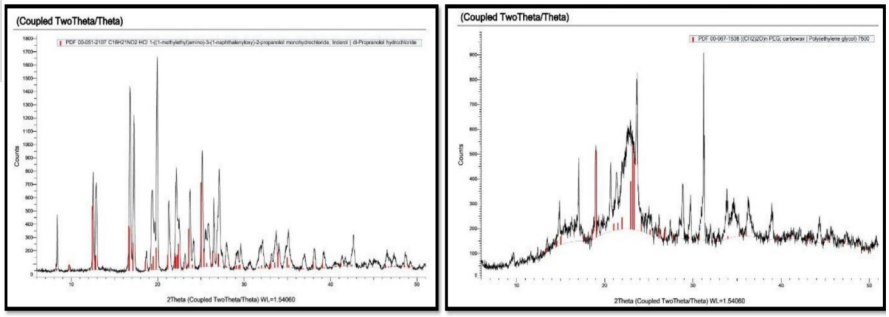


Fig. 4. (A) XRD of Drug (Propranolol Hydrochloride) (B) XRD of a drug resin complex.

Tab. 7. Evaluation of Micromeritics properties of powder blend.

Formulation	Bulk density µg/mL	Tapped density	Compressibility	Hausner's ratio	The angle of repose (θ)
			Index		
F1	0.56 ± 0.04	0.63 ± 0.08	12.45 ± 0.15	1.05 ± 0.05	26.7 ± 0.15
F2	0.55 ± 0.03	0.64 ± 0.11	12.39 ± 0.12	1.08 ± 0.07	25.5 ± 0.18
F3	0.57 ± 0.05	0.61 ± 0.09	13.56 ± 0.14	1.09 ± 0.08	27.7 ± 0.20
F4	0.54 ± 0.04	0.60 ± 0.10	12.34 ± 0.15	1.08 ± 0.06	24.8 ± 0.17
F5	0.52 ± 0.03	0.58 ± 0.07	13.25 ± 0.12	1.05 ± 0.05	24.5 ± 0.16
F6	0.53 ± 0.05	0.59 ± 0.11	12.87 ± 0.13	1.06 ± 0.04	24.9 ± 0.14

formulation was determined using a Pfizer hardness tester and the results are depicted in Table 8.

C. **Weight variation test:** Prepared tablets were evaluated for weight variation and the results are depicted in table no. 7.10 The Percentage deviation of the weight was within 5% as per the monograph.

D. ***In vitro*** **disintegration time:** The disintegration time of the prepared tablet was determined and the results are depicted in Table 8.

E. ***In vitro*** **dispersion time:** Tablets are added to 10 mL of 0.1N HCL at 37 ± 0.5°C. The time required for the complete dispersion of the tablet was measured and the results are depicted in Table 8.

F. **Drug content uniformity:** The content of the prepared tablet was determined spectrophotometrically at 228 nm against blank using a UV-visible spectrophotometer (1800 Shimadzu) and the results are depicted in table 8.

G. **Wetting time:** The time required for water to reach the upper surface of the tablet is noted and the results are depicted in table 8.

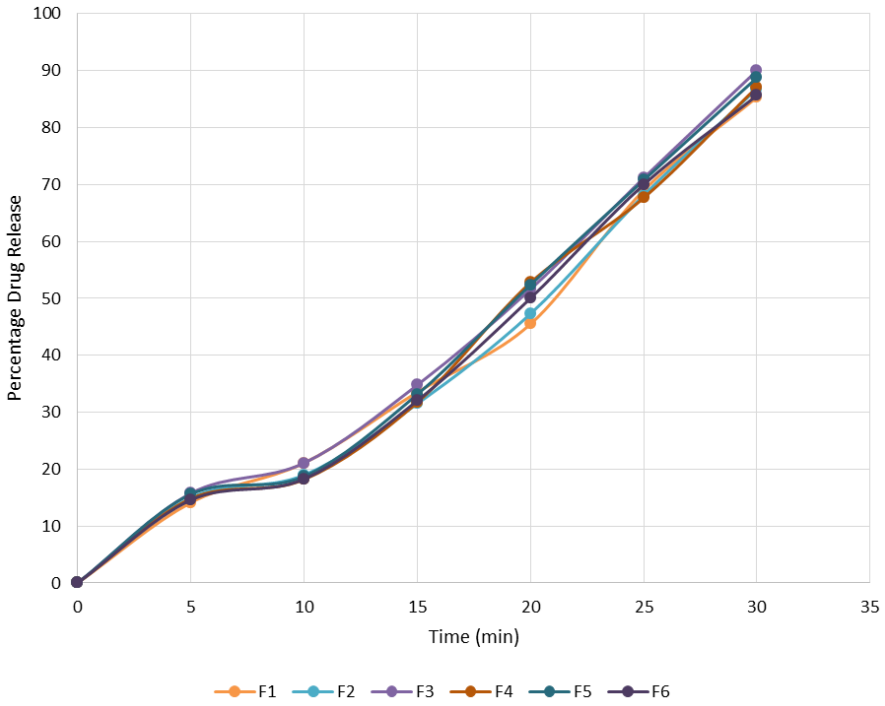
H. **Friability:** The Friability of the prepared tablet is determined using the Roche friabilator, % friability of a prepared tablet < 1% is considered acceptable and the results are depicted in (**Tab. 8.**)

In-vitro **dissolution studies:** A total of Six Formulation was formulated from F1 to F6 using binder and super-disintegrants in varying concentrations. The concentration of Binder (7.5%) in all formulations (F1 to F6) are same but the concentration of Super-disintegrants Kyron T 314 in formulations F1 5%, F2 7.5%, and F3 10%, and the sodium starch glycolate in formulations F4 5%, F5 7.5%, and F6 10%. The formulations F2, F3, and F5 show better drug release compared to other formulations [6]. The

Tab. 8. Characterization of formulated oral dispersible tablet.

Batches	Thickness	Hardness	Weight Variation (mg)	*In-vitro* Disintegration Time (sec)	*In vitro* dispersion time (sec)	Drug Content (%)	Wetting Time	Friability (%)
	(nm)	(Kg/cm2)	(n=3)	(n=3)	(n=3)	(n=3)	(sec)	
	(n=3)	(n=3)						
F1	1.2 ± 0.04	3.1 ± 0.05	Pass	30 ± 0.30	58 ± 0.15	87.78 ± 0.14	26 ± 0.76	0.7 ± 1.01
F2	1.2 ± 0.06	3.5 ± 0.03	Pass	29 ± 0.28	55 ± 0.13	89.62 ± 0.16	27 ± 0.48	0.6 ± 0.89
F3	1.2 ± 0.05	3.4 ± 0.05	Pass	30 ± 0.29	57 ± 0.12	90.17 ± 0.14	26 ± 0.53	0.7 ± 0.99
F4	1.2 ± 0.04	3.6 ± 0.04	Pass	30 ± 0.26	58 ± 0.14	88.98 ± 0.18	27 ± 0.76	0.7 ± 0.98
F5	1.2 ± 0.06	3.6 ± 0.06	Pass	29 ± 0.30	56 ± 0.17	90.10 ± 0.15	28 ± 1.03	0.7 ± 0.49
F6	1.2 ± 0.05	3.1 ± 0.05	Pass	29 ± 0.38	57 ± 0.15	89.56 ± 0.16	27 ± 0.97	0.6 ± 0.78

Fig. 5. Drug release profile of formulated batches.



formulation F3 showed the highest drug release (90.03%) (**Fig. 5**).

CONCLUSION

In the present study using CCD for analyzed swelling time, stirring time, pH, temperature and, resin activation parameters, and the drug loading was found to be 72.88%, 79.72% and, 61.4%. Characterization of the drug was done by performing the melting point, UV spectroscopy, and FTIR spectroscopy. FTIR spectrum of the pure drug was compared with that of the physical mixture of drugs with all the excipients used in the study. The results showed that there were no drug excipients interactions. The melting point was found to be 163o C and from the UV spectral analysis of the drug, the solution indicated the λ max value as 228 nm. We optimized the condition required for maximum drug loading of Propranolol Hydrochloride with Kyron-T 314. All the optimized tablet (MDT) formulations of propranolol hydrochloride (F1 to F6) showed all parameters within the limit as well as good physiochemical properties. The drug release rate of formulated MDTs was also found to be higher as compared to a conventional tablet. Kyron-T 314 10% F3 has hardness (3.4 kg/cm2), friability (0.70%), and wetting time (26 sec), hence tablets formulated with Kyron-T 314 not only increase the rate of dispersion but also increase the rate of drug release. *In-vitro* dispersion time of all formulations was done and observed that there is a decrease in the in-vitro dispersion time with the increase in the concentration of super disintegrant. An in-vitro dissolution study of all the formulations was carried out for 30 seconds and according to the results of optimized formulations was found as the best formulation, which showed the highest drug loading. The work proves that CCD optimization techniques are much helpful for getting optimized products without the need for rigorous experimental work to save time and a better product may be obtained. The methods may be used for developing better ODTs and it may pave the way for further work.

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