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Research Article

PREPARATION AND EVALUATION OF BILAYER TABLET OF PARACETAMOL AND THIOCOLCHICOSIDE: A DUAL APPROACH FOR PAIN MANAGEMENT

Pankaj[1]*, Dr. Mayank Bansal[2], Dr. Rakesh Kumar Gupta[3]

[1]Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan.
[2]Principle & Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan.
[3]Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan.

Corresponding Author*: Pankaj, Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, India,

Email ID: pankajyadav13132@gmail.com

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Abstract

The traditional drug delivery system is not much effective when treating pain. Consequently, there is a gap in the market for a delivery system that can provide a treatment for this disorder. The present study is based on the objective to develop dual release bilayer tablet designed by BBD approach. The bilayer tablet contained an immediate release layer of paracetamol and a sustained release layer of thiocolchicoside. The optimization of the bilayer tablet was done using a three-level, three-factor Box-Behnken design. A total of thirteen formulations of paracetamol and thiocolchicoside were developed based on the design composition of paracetamol, sodium starch glycolate and sodium bicarbonate for the IR layer and thiocolchicoside, HPMC and magnesium stearate for the SR layer respectively. The developed dual release layers were compressed to form a bilayer tablet. The initial characterization and drug-excipient interaction studies were performed initially using infra-red (IR) spectroscopy and X-ray diffraction studies (XRD). Formulations showing good micrometric properties, disintegration and drug release, were selected for final compression of bilayer tablets. Formulation F13 showed the fastest drug release (91.34%) at 60 minutes and quick disintegration time (97 s). The sustained release thiocolchicoside tablet layer (F11-F13) had a hardness that varied from 4.05 to 4.90kg/cm2. Formulation F5 had the highest hardness, whereas F6 showed the lowest hardness. The sustained release layer showing 98.21% of drug release after 10 hours was selected for the compression to bilayer tablet. The developed dual layer tablets were investigated for quality parameters like hardness, percentage friability, weight variation, disintegration and dissolution. A high level of patient compliance is ensured through the current design as the patient does not need to get out of bed at night to take the medication.

Keywords: Thiocolchicoside, Paracetamol, Immediate Release, Sustained Release, Box-Behnken design.

1. Introduction

Paracetamol is white crystalline solid. Comes under BCS Class I. Acetaminophen is the significant metabolite that is produced by phenacetin and acetanilide. In the hepatocyte, paracetamol undergoes 1st order kinetic metabolism via three separate pathways: glucuronidation, sulphation,

and CYPOR, N-acetyl-p-benzoquinone imine, also known as NAPQI, is the reactive metabolite that is produced as a consequence of this final route[1]. Although acetaminophen's exact mode of action is still up for debate, the medicine is often considered an NSAID (nonsteroidal anti-inflammatory drug) due to its ability to block cyclooxygenase (COX) pathways, as stated on its FDA label. According to popular belief, it alleviates pain by acting centrally. The production of prostaglandins is what causes us to feel pain. In peripheral tissues, paracetamol does not inhibit cyclooxygenase, so it does not have any anti-inflammatory benefits[2].

Thiocolchicoside has soothing and analgesic effects and is used for relaxing muscular pain. comes under BCS Class III. It is a potent antagonist of GABA and glycine receptors and a weak antagonist of nicotinic acetylcholine receptors. Thiocolchicoside is a powerful muscle relaxant because of its specific and strong affinity for the GABA-A receptor, which it uses to alleviate muscular contractions by opening the GABA inhibitory channels. The human brain's inhibitory neurotransmitter of choice is GABA. It is applied when you're experiencing aches and pains in your joints, muscles, or rheumatoid arthritis pain[3].

Through the use of solid dispersion, the paracetamol's solubility may be improved. For the formulation of the bilayer tablet, the formulation that had the highest possible solubility and dissolution was chosen as the final formulation.

Solid dispersion (SD)- defined as the dispersion of one or more active ingredients in an inert matrix at solid-state prepared by the melting (fusion), solvent, or melting-solvent method—was first introduced by Sekiguchi and Obi in 1961. Since then, SD-containing drug delivery systems prepared by solvent-emulsion evaporation, hot melting, solvent evaporation, coprecipitation, spray drying, supercritical fluid, and co-grounding, among other techniques[4].

The layered tablet concept has been utilized to develop controlled-release formulations. Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fast-release layer combined with sustained-release layers. Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled- release dosage forms, as the drug is quickly released from the fast-release layer, leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained-release layer[5].

2. Materials and Methods

2.1 Materials

Paracetamol, Sodium Starch Glycolate, Sodium Bicarbonate was supplied by Chemical house of Jaipur college of pharmacy. Thiocolchicoside was obtained from Medipol Pharmaceuticals Pvt. Ltd. HPMC was supplied by Nectar life Science, Hyderabad. Magnesium Stearate, gifted by Signet chemical Corporation Pvt. Ltd. Potassium Dihydrogen Orthophosphate, MCC, Aerosil Hydrochloric Acid obtained by Loba Chem. Pvt Ltd. PEG 6000 and PVP K30 were generously gifted by S. D. Fine Chem Limited (Mumbai, India). Other chemicals were of analytical grade. Double-distilled water was used throughout the studies.

2.2 Methods

A. Preparation of calibration curve in methanol: 100 mg of drug was dissolved in 100 ml of methanol to make the stock solution of 1000µg/ml. Excess amount of solution was taken from this and was dissolved in methanol to make up 100µg/ml solution. Then from this solution excess amount was taken and was dissolved in methanol to make up 20µg/ml solution. Further from this solution excess amount was taken and was dissolved in methanol to make up 2,4,6,8 and 10 µg/ml solution respectively and absorbance was determined at 243 nm using methanol as blank[6].

B. Drug - Excipient Interaction Study: Fourier transform infrared spectroscopy (FT-IR) and differential

scanning calorimetry (DSC) investigations were made to detect possible drug and excipient interactions[7].

C. Fourier transform infrared spectral assignment: The infrared spectra of paracetamol were obtained using an IR Spectroscopy. The infrared chamber was used to scan a specimen pelleted at a resolution of four centimetres per inch with a frequency ranging from four thousand to four hundred per centimetre.

D. 6.1.1.8 X-ray diffraction experiment: To determine if unadulterated paracetamol exhibited crystalline or amorphous behaviour, an X-ray diffraction experiment was conducted under the following conditions: The target is exposed to monochromatized Copper K-α irradiation at room temperature using a forty-kilovolt voltage and a 40 milliamperes power. The data was collected in scanned mode at a rate of 20 per second with a step size of 0.01 degrees. A range of thirty to three hundred degrees was scanned.

E. 6.1.1.9 DSC: For the DSC analysis of the pure drug, the DSC 60 Simadzu were used. The sample has been heated in an open aluminium pan at a rate of ten degrees Celsius per minute at temperatures ranging from thirty to three hundred degrees Celsius while being subjected to a NO2 circulation rate of forty millilitres per minute of time.

2.3 Solubility enhancement of drug paracetamol by using, solid dispersion

Drug and poloxomer 188 (1:3) were weighed and mixed using mortar and pestle for the preparation of physical mixture. mixture were passed through sieve of 50 #. In phosphate buffer 10ml sample having concentration of pH 6.8 and solubility was determined by adding drug in excess amount (10mg) in it. The solution was kept at 25°C for 24 hours in mechanical shaker and in and solubility analysis were performed[8].

2.4 Experimental design for formulation development

The current study used thirteen runs, three factors, and three levels of Box-Behnken for the purpose of developing second order polynomial models and conducting an analysing of the quadratic response surface in order to optimise the bilayer tablets. The software utilised was design expert program (Test Version 11.05.0, Stat Ease Inc., Minnesota) [9]. The factors evaluated in the present work are Concentration of Paracetamol (mg), Sodium Starch Glycolate and Sodium Bicarbonate for immediate release layer and Concentration of Thiocolchicoside (mg), HPMC (mg) and magnesium stearate (mg) for sustained release at low medium and high values. The dependent variables/responses were Q+5% (% drug release) and disintegration time (seconds) for immediate release layer and % drug release for sustained release layer. The results obtained for each response were fitted to a linear model and a quadratic model, described by the following polynomial equations below. This has been illustrated in table 1 and table 2:

Linear equation: $y = a + b1X1 + b2X2 + b3X3$

Quadratic equation: $Y = \beta0 + \beta1A + \beta2B + \beta3C$.....

where y is the measured response, b1, b2, b3, and β0–β3 are the regression coefficients, and X1, X2, and X3 are the independent factors. The models were validated by analysis of variance (ANOVA), lack of fit, and multiple correlation coefficient (R2) tests.

Table 1: Variables and their levels in box-behnken design for immediate release paracetamol

Independent Variables	Levels		
	-1 (Low)	0 (Medium)	+1 (High)
A = paracetamol solid dispersion(mg)	360	240	480
B = Sodium Starch Glycolate (mg)	5	12.5	20
C = Sodium Bicarbonate	10	15	20
Dependent Variables			
Y1 = Q+5% (%)	Maximize		
Y2 = Disintegration Time (Seconds_	Minimize		

Table 2: Variables and levels of box-behnken design for sustained release thiocolchicoside

Independent Variables	Levels		
	-1 (Low)	0 (Medium)	+1 (High)
A = Thiocolchicoside	5	7	9
B = HPMC	1	4	7
C = Magnesium Stearate	2	3	4
Dependent Variables			
Y1 = % Drug Release (%)	Maximize		

2.5 Preparation of immediate release paracetamol layer

A solid dispersion consisting of paracetamol and Poloxomer 188 at a ratio of 1:3 was sorted through a 40# sieve. Lactose and sodium starch glycocholate were also sifted through there. A starch binder was integrated into the powder that had been sifted. In the third step, granulation, all of the materials that had been sifted were put through a mortar pestle, and then granules were made by adding one to two drops of distilled water to the powder that had been sifted. It took 20 degrees Celsius in a heated aired oven to dry the granules to a percentage decrease of dryness of between one and two percent. The dry grains were filtered using a 20# mesh screen**.** The addition of intra-granulation material was filtered via a sieve with a 60-pound capacity, then added to step 4 and mixed for two minutes as part of the process. In order to compress the tablets, a single punch machine was used throughout the preparation process. Table 3 provide compositions for different experimental batches[9].

2.6 Preparation of sustained release thiocolchicoside layer

Thiocolchicoside and Microcrystalline Cellulose were allowed to pass through a sieve with a number of forty. The addition of the binder: Hydroxypropyl methyl cellulose (HPMC) was added to the powder that had been separated. **I**n the third step, granulation, all of the materials that had been sifted were put through a motar pestle, and then granules were made by adding one to two drops of distilled water to the powder that had been sifted. Granules were dried in an oven with hot air at a temperature of forty degrees Celsius until a loss of drying of one and a half to two percent was attained. The dried granules were sized by passing them through a sieve with a 20# mesh. The addition of intra-granulation material was filtered via a sieve with a 60-pound capacity, then added to step 4 and mixed for two minutes as part of the process. The tablet was made by use of a single punch machine throughout the preparation process. Table 4 provide compositions for different experimental batches[10].

A. Precompression Parameters- Evaluation of Paracetamol and Thiocolchicoside Granules Blend: The paracetamol-granules & Thiocolchicoside Granules of all batches were evaluated for density (bulk density and tapped density), angle of repose, Hausner's ratio and compressibility index.

B. Disintegration test for immediate release layer: The disintegration test employed six tablets and Disintegration testing equipment was maintained at 37±0.5°C in PO_4^{2-} buffer solutions with a pH of 6.8. The tablet were put in the equipment baskets and the disintegration time was carefully noted.

C. In vitro drug release: In vitro drug release of the developed tablet formulations was examined using USP type 2 dissolving test apparatus. A temperature range of 37 ±0.5 degrees Celsius was used in the research. The study used a PO_4^{2-} buffered in a volume of 900 millilitres with a pH of 6.8. The experiment included sixty minutes of administration of the paracetamol IR release layer and eight hours of administration of the thiocolchicoside SR layer. Each time a certain length of time elapsed, portions

were drawn out of the reservoir and replaced with a volume of fresh buffer of the same size. To determine the concentration of thiocolchicoside, the absorbance of the samples was measured at two different wavelengths: 234 and 259 nanometres[11].

D. Optimization and validation: Validation of the polynomial equation using statistical analysis was accomplished by analysing the ANOVA specification. Subsequently, the best possible values for every variable were estimated using the numerical and graphical optimisation tool.. This was accomplished by giving the program with a predetermined criterion of value.

E. Preparation of bilayer tablets of paracetamol and thiocolchicoside: The wet granulation technique was used in order to manufacture Dual Release Drug Delivery System of paracetamol and thiocolchicoside. The process of wet granulation was used in order to granulate both of the layers. In the beginning, the granules of immediate-release paracetamol were put into the compression tool. A mild compression force was used to punch the tablets that were part of the initial layer. After this layer had been punched, granules that had been created using wet granulation for the thiocolchicoside powder mix were put on top of it. In order to get bilayer tablets, Punching each layer simultaneously required an increase in compressive strength. Following the incorporation of some dye colour into the sustained release layer of thiocolchicoside, the two layers were able to be separated from one another with great clarity. In the subsequent step, the bilayer tablets that had been manufactured were put through quality control tests[12].

F. Post-compression analysis of the prepared bilayer tablets: As per pharmacopoeial procedures all batches of tablet were characterized for thickness, weight variation, hardness and friability & In vitro drug release.

2.7 Stability Test

Stability test was performed by storing the prepared formulations at 40°C, RH 75% for a defined period of time. At regular intervals of two months, the tablets were examined and analysed for a variety of factors, including characteristics such as their hardness, disintegration, and pharmacological composition[13].

3. Result and Discussion

Paracetamol dissolved in methanol. Calibration curves were subsequently generated in methanol. The 243 nm absorption maxima of the drug in methanol were established by scanning a sample with a concentration of 10 µg/ml, as seen in figure 1. In preparing the paracetamol drug calibration curve in methanol, the regression value was determined to be 0.997, indicating that the drug is linear. It was from the standard calibration curve that the concentration ranging was selected for the medications where Beer's law was enforced. For paracetamol, the range was determined to be 2 to 10 µg/ml. A three-reading average absorbance value and standard deviation (SD) were calculated. We discovered that the slope is 0.1132.

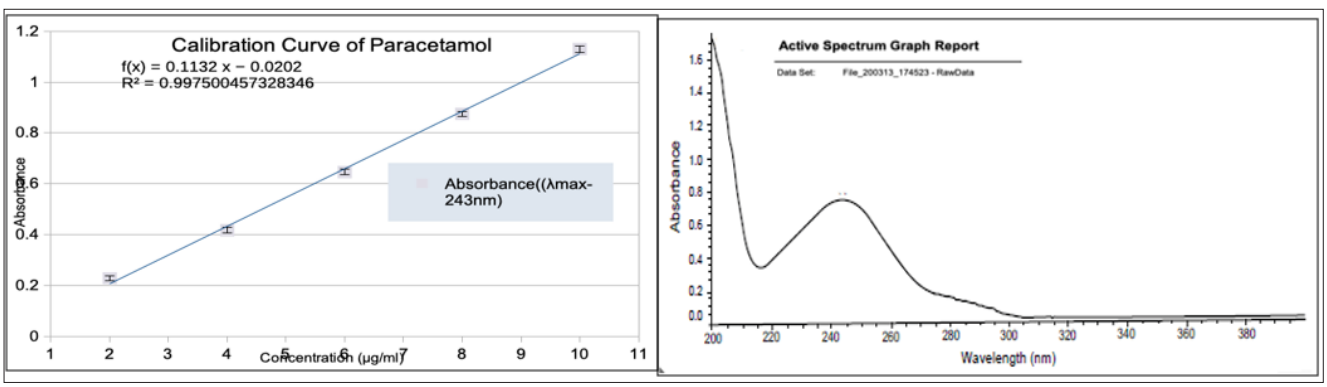

Figure 1: Calibration Curve for Paracetamol and λmax of Paracetamol in methanol

3.1 Fourier transform infrared spectroscopy (FTIR)

Pure drug FTIR analysis Spectrum (figure 2) demonstrates the presence of paracetamol. This peak is exhibited in the FTIR spectra of the pure medication, and it is responsible for the aromatic C-H stretching that is seen at 2880.63 cm-1. There is a representation of asymmetric stretch of the C-H bond for the band at 2945 cm. The N-H band starts to show up around 3326.35 cm-1. At 3162.35 cm-1, the O-H band may be seen. The C=O band may be picked up at 1654.87 cm-1. The frequency of the C=C band is 1736.42 cm-1. At 1246.02 cm-1, the C-O band may be seen. At 1097.11, the C-N stretching band is being broadcast.

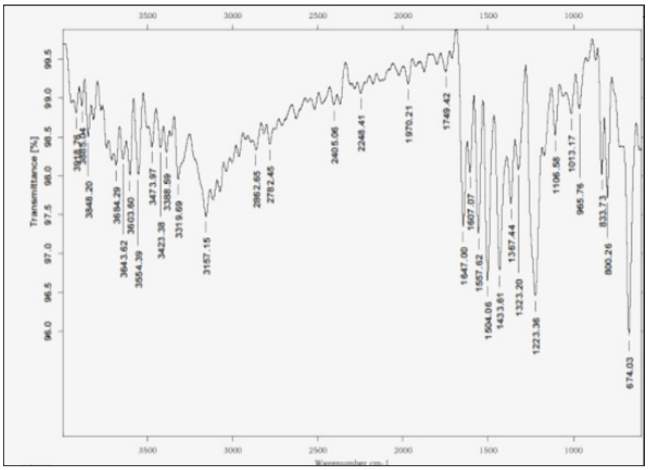

Figure 2: IR spectra of pure drug paracetamol

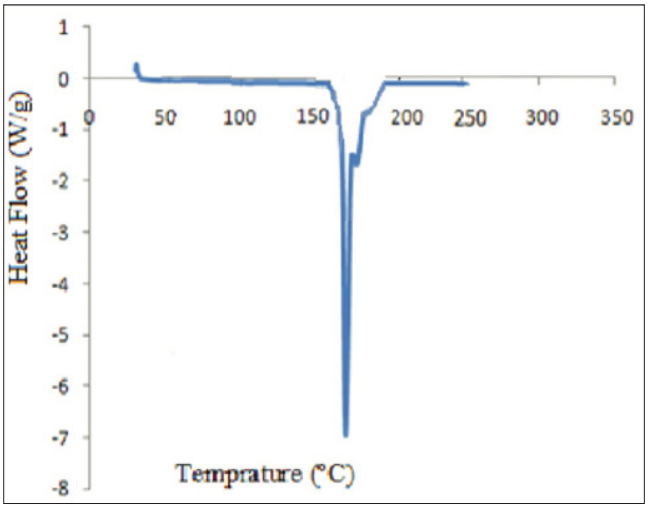

Figure 3: DSC Study of Paracetamol

3.2 Differential scanning calorimetry (DSC)

Research Conducted Using DSC: Figure 3 depicts the DSC of paracetamol which displays an endothermal peak at 169 degrees Celsius, which corresponds to the intrinsic melting temperatures, the purity of the medication paracetamol is represented by this peak-to-peak.

3.3 Calibration graph of thiocolchicoside in PBS pH 6.8

The calibration graph for the pure drug thiocolchicoside has been Prepared in PBS with a pH of 6.8. For the pure drug PBS with a pH of 6.8, the absorption maximum has been discovered at 259 nm for a sample concentration of 20 µg/ml, Consequently, the calibration curve for the thiocolchicoside has been created in PBS with a pH of 6.8, as shown 4. The value of regression that was achieved was 0.999, which suggests that linearity was present.

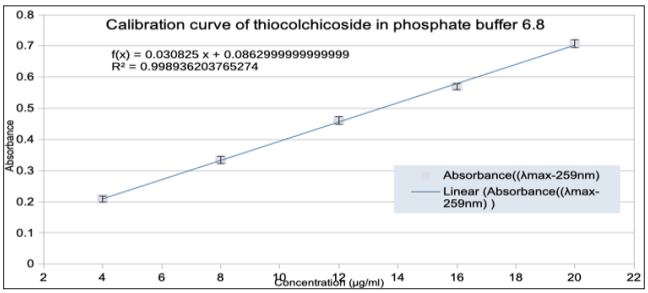

Figure 4: Calibration Curve of Thiocolchicoside in PBS pH 6.8

3.4 FT- IR spectra of thiocolchicoside

Various molecular verification have been conducted using FTIR spectroscopy on thiocolchicoside. The N-H stretch vibration at 3285 cm-1, the thio ether band stretch at 2331 cm-1, and the carbonyl band at 1550 cm-1 are all visible in the thiocolchochicoside spectrum. The tropane ring is also visible at 1643 cm-1. This proves that the thiocolchicoside medication is pure. As shown in figure 5, FTIR is depicted schematically.

3.5 Differential scanning calorimetry (DSC)

Thiocolchicoside has an inherent melting point of 209°C, as seen by the endothermic peak in the DSC curve (Figure 6).

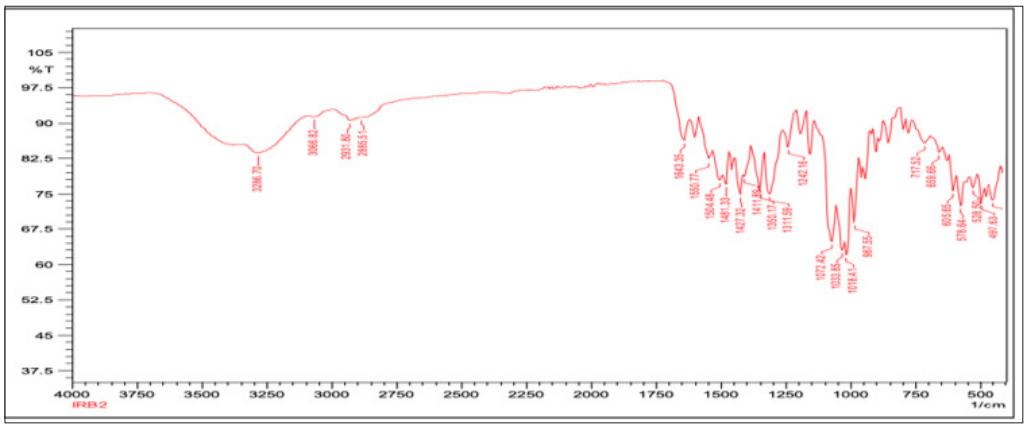

Figure 5: FT-IR spectroscopy of thiocolchicoside

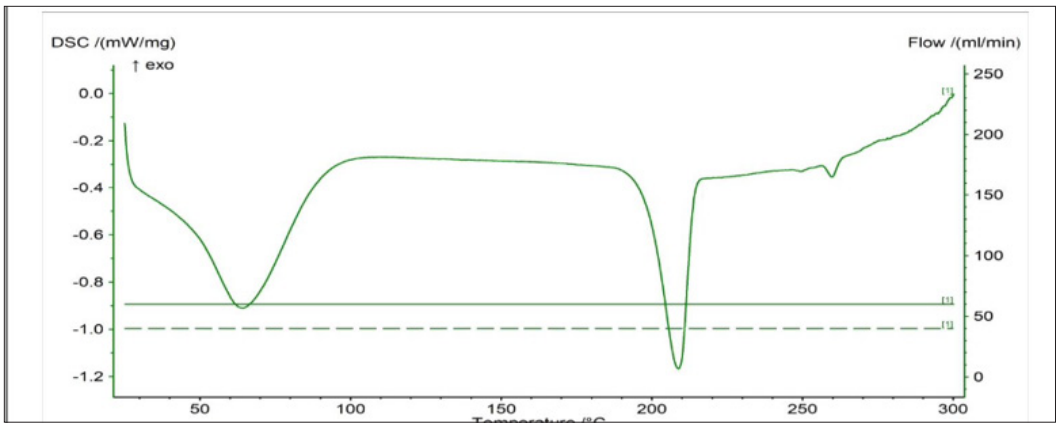

Figure 6: DSC study of thiocolchicoside

Table 3: Combination of immediate release layer for paracetamol tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Solid Dispersion (Paracetamol & Poloxomer 188) (1:3)	360	480	480	240	360	240	240	360	480	240	480	360	360
MCC	15	15	15	15	15	15	15	15	15	15	15	15	15
Lactose Monohydrate	141	26	13.5	223.5	138.5	266	251	151	23.5	293.5	16	136	126
SSG	5	5	12.5	12.5	12.5	5	20	5	12.5	12.5	20	20	20
$NaHCO_3$	20	15	20	20	15	15	15	10	10	10	15	10	20
Starch	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight	550	550	550	550	550	550	550	550	550	550	550	550	550

Table 4: Combination of sustained release layer for Thiocolchicoside layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Thiocolchicoside	7	7	5	7	9	5	7	9	5	9	9	7	5
MCC	15	15	15	15	15	15	15	15	15	15	15	15	15

Lactose Monohydrate	37.5	39.5	34.5	31.5	34.5	40.5	33.5	32.5	38.5	31.2	36.5	35.5	36.5
HPMC	1	1	7	7	4	1	7	4	4	7	1	4	4
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate	4	2	3	24	2	23	2	4	2	3	3	3	4
Indigo Caramine Blue	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total Weight	80	80	80	80	80	80	80	80	80	80	80	80	80

Table 5: Micromeritic study of blend of paracetamol tablet

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.52	0.55	5.34	1.04	23.5
F2	0.42	0.48	12.1	1.12	28.9
F3	0.62	0.67	7.35	1.006	24.21
F4	0.46	0.53	12.94	1.13	32.01
F5	0.58	0.61	5.50	1.05	18.01
F6	0.47	0.50	4.94	1.04	17.06
F7	0.550	0.557	6.25	1.13	18.02
F8	0.240	0.245	2.04	1.02	14.6
F9	0.37	0.42	1.71	1.09	19.2
F10	0.37	0.42	1.71	1.09	21.34
F11	0.62	0.67	7.34	1.07	28.5
F12	0.42	0.48	9.29	1.11	22.64
F13	0.35	0.41	14.2	1.15	23.7

Table 6: Micromeritic study of dry blend of thiocolchicoside tablet

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.27	0.32	12.5	1.14	21.68
F2	0.33	0.36	5.55	1.16	19.36
F3	0.31	0.33	6.06	1.06	18.36
F4	0.32	0.37	13.5	1.16	19.17
F5	0.30	0.36	8.33	1.20	20.68
F6	0.32	0.35	8.57	1.09	21.6
F7	0.30	0.32	6.25	1.06	24.3
F8	0.31	0.33	6.06	1.06	14.86
F9	0.32	0.34	5.88	1.06	21.2
F10	0.30	0.31	3.22	1.03	19.6
F11	0.33	0.36	8.33	1.09	17.2
F12	0.32	0.34	5.88	1.06	14.1
F13	0.30	0.32	6.25	1.06	16.9

3.6 Pre-compression parameters of immediate release layer and sustained release layer

The paracetamol immediate release layer was evaluated for angle of repose, bulk density, tapped density, Hausner's ratio (HR), and compressibility index. The bulk density was found in the range of 0.240–0.62 g/ cm3 . The tapped density was range 0.245–0.67 g/cm3 . The angle of repose varied from 14.6° to 32.01°. The compressibility index was in the range of 1.71–12.94%. The HR was in the range of 1.02–1.13 shown in Table 5. it was determined that the flow characteristics of F1, F3, F5, F6, F7, F8, F9, F10, F12, and F3 were excelent, while the flow properties of F2 and F11 were very good. The F4, on the other hand, had the greatest value for angle of repose, indicating that its flow qualities were satisfactory. The sustained release layer of thiocolchicoside was prepared by the wet granulation method the powder was evaluated for angle of repose, bulk density, tapped density, HR, and compressibility index. The bulk density was found in the range of 0.27–0.33 g/cm3 . The tapped density was range 0.31–0.37 g/cm3. The angle of repose varied from 14.1° to 24.3°. The compressibility index was in the range of 3.22–13.5%. The HR was in the range of 1.03–1.20 shown in Table 6.

3.7 Post compression parameter of immediate release layer and sustained release layer

The paracetamol immediate release layer post compression parameter was evaluated for hardness, friability, weight variation, and disintegration time. The hardness of tablet of each formulation was found in the range of 4.0±0.200–4.14±0.124 kg/cm2. The friability was in the range of 0.75%. - 0.86 %. The weight of tablet of each formulation varied from 537-±1.38 mg to 562±1.44 mg. All tablets were within the pharmacopeia limits of the weight. The weight of all tablets was found to be uniform with low standard deviation valve. The disintegration time of all tablets was found in the range of 1.37 min–2.53 min, all of the manufactured batches were subjected to dissolution tests, which yielded results ranging from 80.4% to 92.15% (figure 7). This led to the assessment of the paracetamol tablet's quick release layer, parameter shown in Table 7. The thiocolchicoside sustained release layer post compression parameter was evaluated for hardness, friability, weight, and drug release. The hardness of tablet of each formulation was found in the range of 4.20±0.165– 4.90±0.139 kg/cm2 . The friability was range 0.29%–0.71%. The weight of tablet of each formulation are 552 mg. The weight of all tablets was found to be uniform all tablet was within the Indian Pharmacopoeia limits of the weight. A cumulative drug release ranging from 98.32% to 101.6% (figure 8) was discovered. As a result, several bilayer tablet batches were made and tested, shown in Table 8. ,

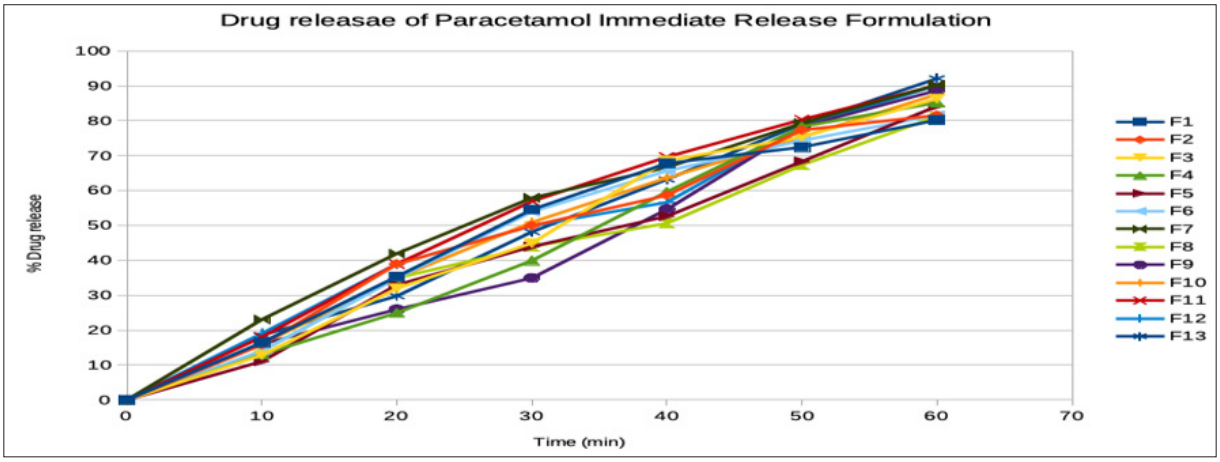

Figure 7: In-Vitro Drug Release Profile of Paracetamol Immediate Release Tablet Formulations

Table 7: Post compression characteristics of immediate release paracetamol

Formulation Code	Hardness (kg/cm2)	% Friability	Weight Variation (mg)	Disintegration Time (min)	Q+5%
F1	4.11	0.75	557	2.31	80.2
F2	4.0	0.82	554	2.3	81.6
F3	4.03	0.80	541	1.45	86.32
F4	4.05	0.76	551	1.46	85.2
F5	4.01	0.86	546	1.55	84.18
F6	4.11	0.81	562	2.17	81.6
F7	4.12	0.82	554	1.45	90.3
F8	4.14	0.84	552	2.53	81.26
F9	4.05	0.75	550	2.30	88.71
F10	4.06	0.76	541	2.34	87.6
F11	4.10	0.82	557	1.45	90.2
F12	4.08	0.80	537	2.12	90.12
F13	4.0	0.71	546	1.37	92.10

Table 8: Post compression characteristics of sustained release thiocolchicoside formulation

Formulation Code	Hardness (kg/cm2)	% Friability	Weight Variation (mg)	% Drug Release
F1	4.71	0.60	552	101
F2	4.30	0.71	552	99.47
F3	4.22	0.53	552	98.32
F4	4.31	0.41	552	98.45
F5	4.90	0.47	552	100.8
F6	4.05	0.56	552	101.6
F7	4.69	0.65	552	99.90
F8	4.64	0.53	552	100.26
F9	4.75	0.29	552	100.01
F10	4.12	0.43	552	99.62
F11	4.20	0.56	552	101.2
F12	4.44	0.44	552	100.02
F13	4.40	0.58	552	99.10

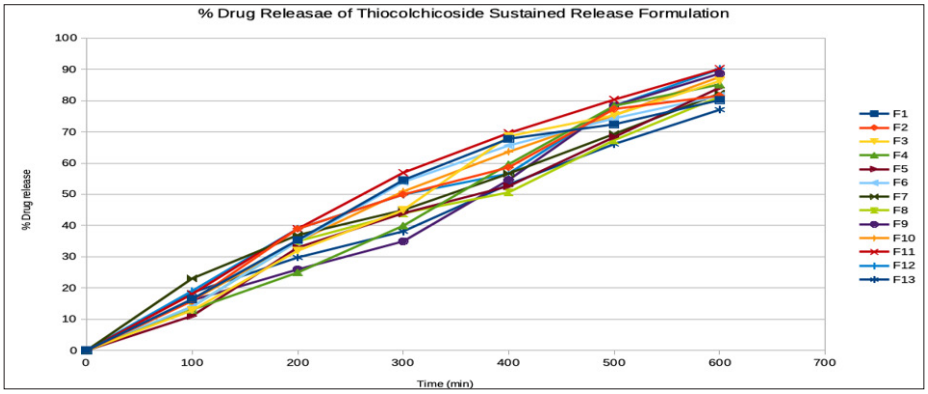

Figure 8: In-Vitro Drug Release Profile of Paracetamol Immediate Release Tablet Formulations

3.8 Statistical evaluation of Immediate Release paracetamol Layer

The dependent variables/responses were Q+5% (% drug release) and disintegration time (seconds) for immediate release layer and % drug release for sustained release layer was applied to optimize the formulation A total of 13 experimental runs were carried out based on the experimental matrix of BBD, which is shown in Table 1 &2. Data of the responses Y1 and Y2 were fitted to the linear model for IR layer, Validations of the models were performed by analysis of variance (ANOVA) test, lack of fit tests, and correlation coefficients (R2). The results of ANOVA and lack of fit tests for evaluation of the models for each of the three responses are shown in table 9. ANOVA was used to test the statistical significance of the ratio of mean square variation due to regression and mean square residual error. The model developed for Q+5% acquired a high level of significant, as shown by the F distribution of 36.66 (p value <0.0000225). The expected R2 value of 0.85188 and the modified R^2 value of 0.899163 were in good agreement, with a difference of less than 0.2 between the two. It was determined that 14.3578 was an appropriate accuracy. The model was found to be suitable, as shown by the PRESS value of 27.42855. The F-Value of 14.67729 indicated that the model developed for the natural logarithm of the disintegrating duration was statistically significant. The statistical credibility of the model is indicated by a p-value that is less than 0.0500. Table 9 provide a summary of the values that were obtained.

3.9 Statistical evaluation of sustained release thiocolchicoside Layer

Y1 were fitted to the second-order quadratic model. it was determined that the model generated for the % of released drugs was significant based on the F-Value of 8.22 (p-value <0.0500). The Expected R^2 value of 0.3959 and the modified R^2 value of 0.7831 exhibited a reasonable degree of acceptance, as one would expect; that is,that is to say, the difference is more than 0.2. The value of 10.4687 was determined to be enough precision, which was larger than 4, indicating that appropriate signal and model could be used for the purpose of traversing the design space successfully. According to the PRESS value of 3.503259, the model is suitable for the data shown in table 10.

Table 9: ANOVA for (a) Q+5% (Y1) and (b) disintegration time (Y2) for IR tablet

Source	Y1				Y2					
	Sum of Squares	DF4	Mean SquareE	F-Valuef	p-Value	Sum of Squares	DF4	Mean SquareE	F-Valuef	p-Value
Model	171.1772	3	57.0590 6	36.667 9	2.25E-05	2.0173	3	0.672433	14.6772 9	0.00082
A	0.73205	1	0.73205	0.4704 38	0.510066	0.00605	1	0.00605	0.13205 4	0.724701
B	169.372	1	169.372	108.84 37	2.51E-06	1.14005	1	1.14005	24.8840 3	0.000751
C	1.073113	1	1.07311 3	0.6896 15	0.427774	0.8712	1	0.8712	19.0158	0.001822

R^2	0.924372	0.830291
Adjusted R^2	0.899163	0.773721
Predicted R^2	0.851883	0.682915
PRESS	27.42855	0.770398
Adequate Precision	14.35788	11.91781

Table 10: ANOVA % drug release for SR tablet

Source	Y				
	Sum of Squares	DF4	Mean SquareE	F- Valuef	p-Value
Model	5.170475	6	0.861746	8.22274	0.010764
A	0.1682	1	0.1682	1.604957	0.252156
B	3.2768	1	3.2768	31.26708	0.001391
C	0.0128	1	0.0128	00.122137	0.738667
Residual[a]	0.628802	6	0.1048		
Cor Total[b]	5.799277	12			
R2	0.891572				
Adjusted R2	0.783145				
Predicted R2	0.395914				
PRESS	3.503259				
Adequate Precision	10.46087				

3.10 Response surface analysis of formulation characteristics

Response surface analysis of formulation of immediate release paracetamol of Q+5% by design-expert software.

According to the provided equation, the parameters influencing Q+5% were the concentrations of paracetamol (A), sodium starch glycolate (B), and sodium bicarbonate (C) (p=0.0008)

Q+5% = 72.07 + 0.3025*A + 4.356*B + 0.356*C (r2 = 0.9265)

analysis and validation using ln instead of log transformation for disintegration time, as suggested by the software. A, Paracetamol concentration, B, and C, SSG and $NaHCO_3$ respectively, affected disintegrating duration (P = 0.00082). Based on the provided equation,

ln(Disintegration Time) = 4.57 + 0.025*A – 0.367*B-0.30*C (R2 = 0.9255)

Response surface analysis of percent drug release of sustained release thiocolchicoside by design expert software:

% Drug Release = 99.71- 0.135*A- 0.54*B- 0.03*C (r2 = 0.9)

Both a counter plot (two-dimensional) and a RSM (three-dimensional) has been created using DoE software in order to carry out the response surface analysis of product features. The three-dimensional response surface plots and two-dimensional contour plots are graphical representa- tions of the regression equations and express two independent variables at once against each response. Thus, the statistically significant relationship between the dependent and independent variables was further interpreted using response surface analysis [14]. In all the response surface and contour plots, the factors showing the least significant values were fixed at their middle levels. With a constant dosage of paracetamol. Q+5% (Y1) was positively affected (Figure. 11&12) by the concentrations of $NaHCO_3$ and SSG, Paracetamol concentration had a little positive influence on ln (disintegration time), whereas SSG and bicarbonate concentration had

negative effects, according to the values and signs of the coefficients. Nevertheless, ln (disintegrating duration) was unaffected by the concentration of API (A). While holding the Paracetamol concentration constant, we investigated how Y2 was affected by changes in the concentrations of SSG (B) and $NaHCO_3$ (C) (Figure 9& 10)

While the concentration of thiocolchicoside remained constant, (Figure 13,&14) shows the effect of changing the concentration of magnesium stearate and HPMC on the percentage of drug release expressed as Y. A high r2 score of 0.9 indicated that the data was well-fit. The percentage of medication release was unaffected by the concentration of API (A). Reduced medication release accompanied an increase in HPMC concentration. Having a solvent presence makes the polymer chain more mobile. The outcome is a gel that has swelled and become rubbery from a glassy matrix. The viscosity rises with increasing concentration, which in turn slows the drug diffusion coefficient. On top of that, the hydrophobic characteristic of magnesium stearate means it creates a coating on the surface of API and excipients, keeping floating in fluid medium. This makes the formulation less wettable, which in turn slows down the dissolving rate.

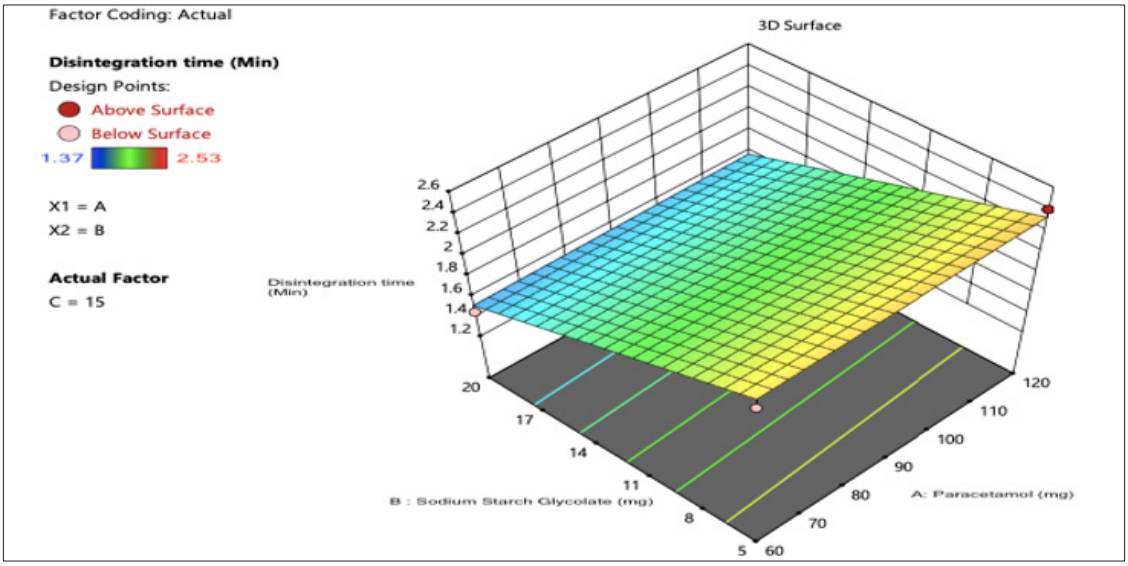

Figure 9: Response surface graph showing consequence of concentration of paracetamol and varying concentration of sodium starch glycolate and sodium bicarbonate on disintegration time

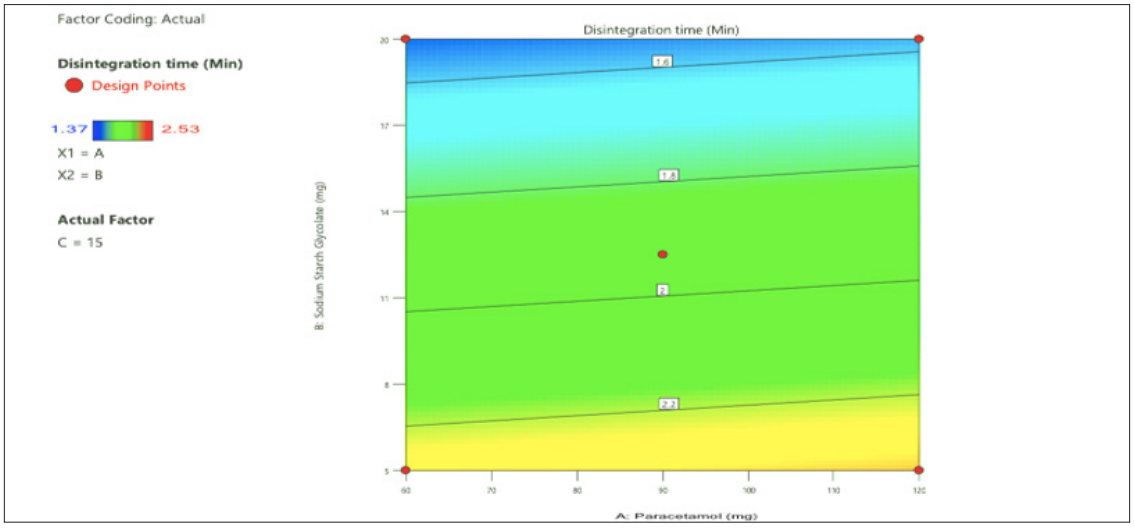

Figure 10: Contour plot (2D) correlating response factor of formulation development of immediate release paracetamol on disintegration time

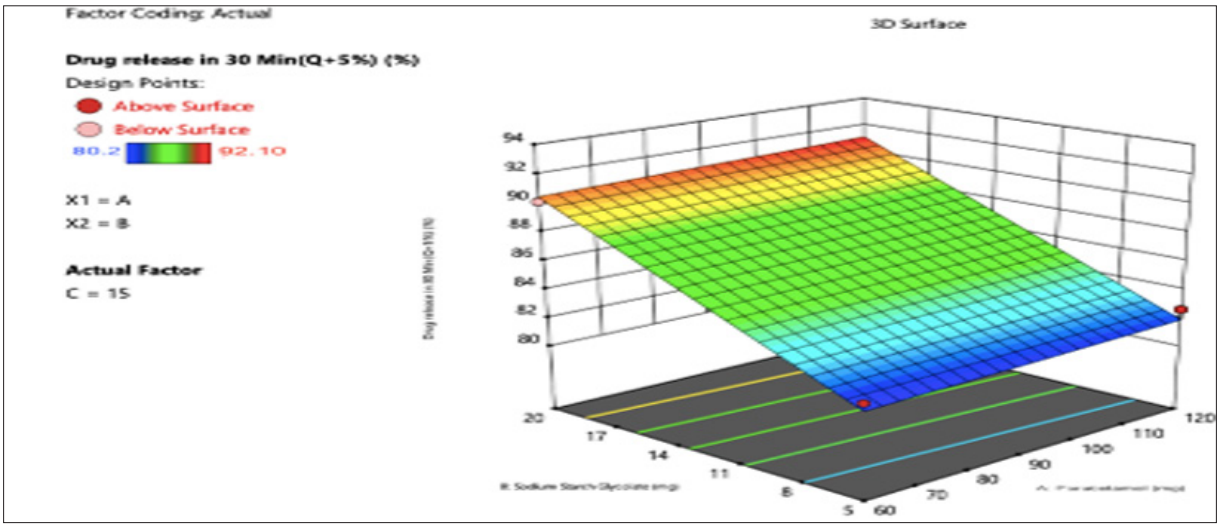

Figure 11: Response surface graph showing varying concentration of sodium starch glycolate and Paracetamol on drug release

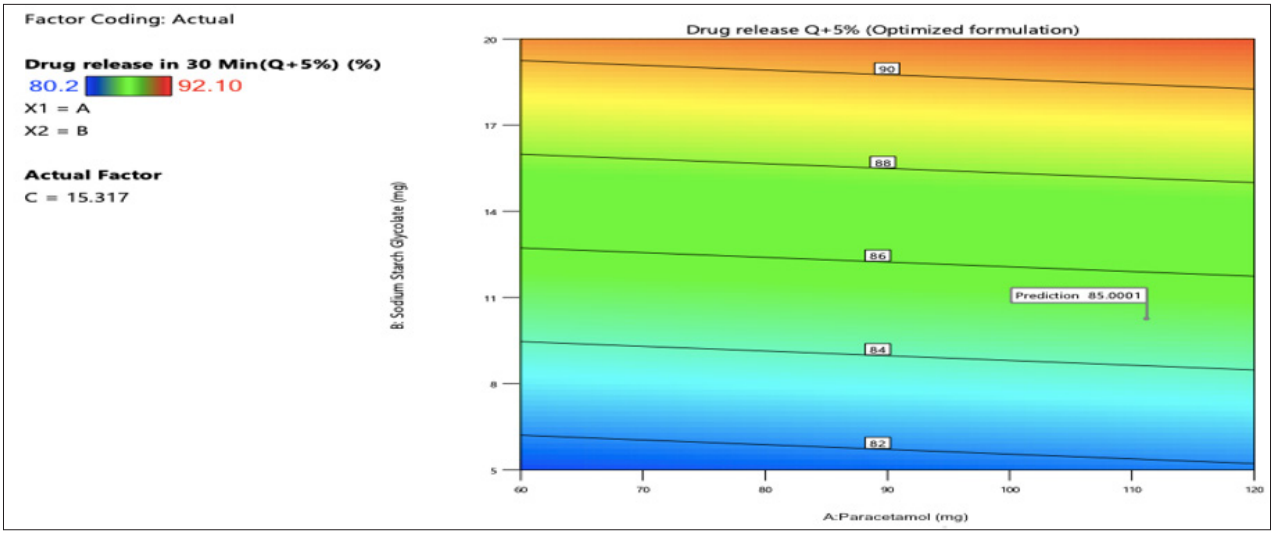

Figure 12: Counter Plot (2D) correlating the response factors for formulation development of immediate release Paracetamol layer on Q+5%

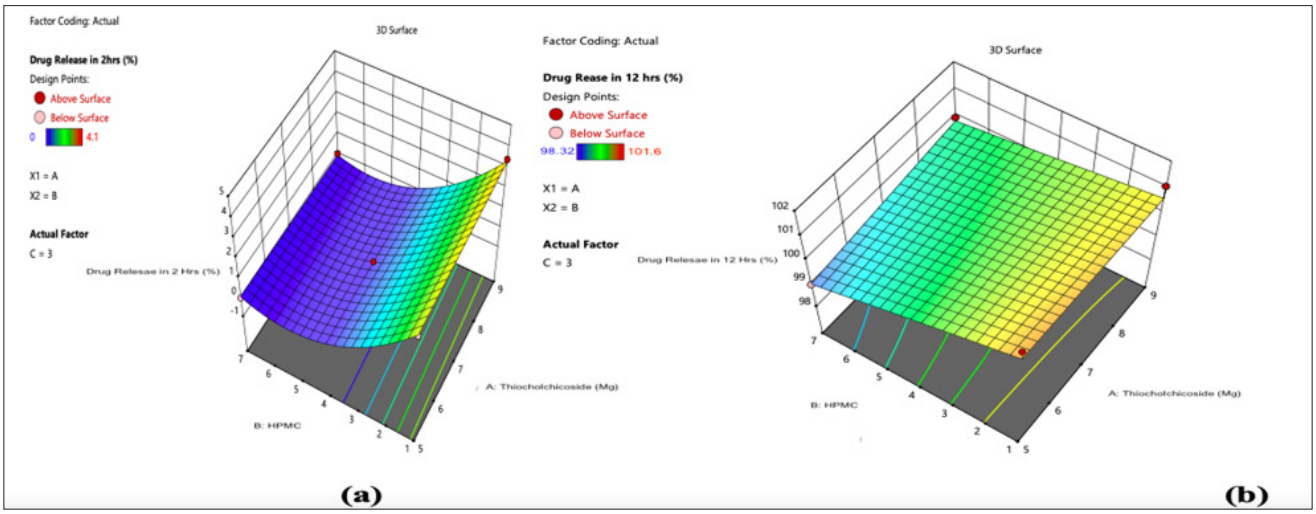

Figure 13: Response surface graph showing consequence of (a) concentration of thiocolchicoisde for drug release in first two hours (b) concentration of thiocolchicoside for drug release in 12 hours

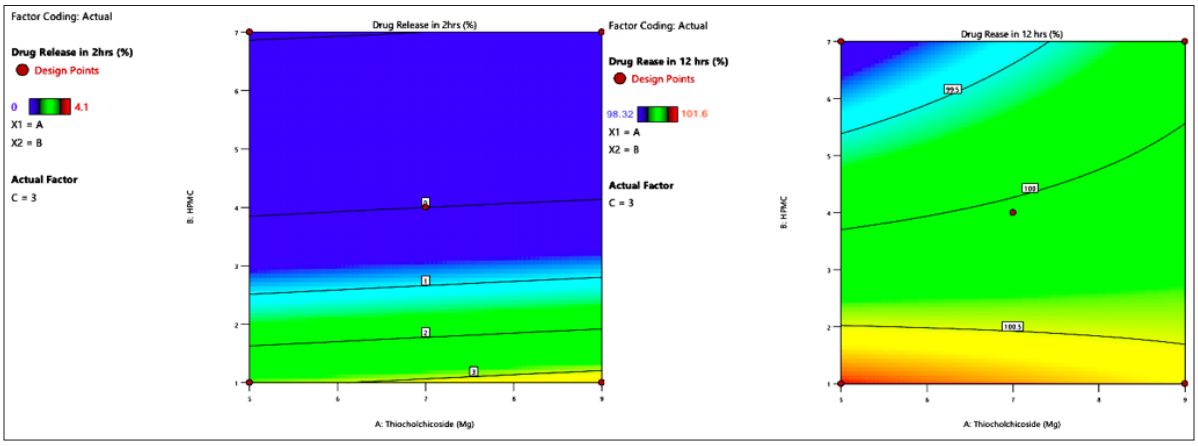

Figure 14: Coulter counter plot correlating the response factor for formulation development of sustained release thiocolchicoside layer on % drug release

3.11 Optimization of formulated layer

With the use of the maximum Q+5% and the lowest disintegration time, the Design-Expert program investigated possible formulation optimisations. Paracetamol immediated release layer (Formulation 13) and sustained release layer (Formulation 5) were thus chosen.

3.12 Preparation & evaluation of bilayer tablet of paracetamol and thiocolchicoside

The bilayer tablet's final formulation was made. To guarantee the tablets' authenticity, they underwent a quality control test. The tablet's surface was flat and smooth. They were white, biconvex, and elegant. One could tell the two layers apart. The prepared tablet did not exhibit any signs of chipping. The typical dimensions were measured to be 4.89±0.0098 cm for thickness and 12.36±0.0098 cm for average diameter. The produced tablet had a mean hardness of 4.87 ± 0.1022 kg/cm² and an observed % friability of 0.45, both of which were within the allowed range. There was an average weight of 670 milligrammes per pill. Weight fluctuation was within acceptable parameters. Within the acceptable range, the disintegrating time of the IR layer was measured at 2 minutes and 92 seconds.

3.13 In vitro drug release study of bilayer tablet

Following a two-hour period in a buffer with a pH of 1.2 hydrochloric acid, the in vitro study was carried out in a buffered solution with a pH of 6.8 phosphate. In accordance with the parameters of the research, it was necessary to examine the release of the medication after an initial lag period of two hours, during which the drug would be in the form of stomach fluid. Figure 16 & 17 illustrate the different release kinetics that are associated with each layer of the final formulation. A rapid release of paracetamol was seen after 40 minutes of dissolution, with a release rate of 91.34% in one hour, according to the results obtained from in vitro dissolution.

One possible explanation is that sodium starch glycolate has a higher capacity to absorb water, which causes a dramatic rise in volume and, a quicker disintegration and dissolution clearly shown in table 7 and 8, respectively. Because of its effervescence properties, The production of CO_2 by baking soda, increases the internal pressure of the formulation, facilitating the rapid release of its constituents. Its dual function of absorbing moisture and easing medication release worked in tandem.

After an interval of 1 hour, just 4.92 percent of the thiocolchicoisde was released. Reduced medication release accompanied an increase in HPMC concentration. Having a solvent presence makes the polymer chain more mobile. The outcome is a gel that has swelled and become rubbery from a glassy matrix. The viscosity rises with increasing concentration, which in turn slows the drug diffusion coefficient. On top of that, the hydrophobic characteristic of magnesium stearate means it creates a coating on the surface of API

and excipients, keeping floating in fluid medium. This makes the formulation less wettable, which in turn slows down the dissolving rate. After twelve hours of research, the SR layer of thiocolchicoside continued to released drug in a consistent manner, with 98.21% of the drug being released on a regular basis. Consequently, the formulation was able to fulfil the criterion by delivering an instant release during the initial hour and a continuously released at the time of ten hours after the drug had passed through the stomach area. Figure 15. illustrates the graph.

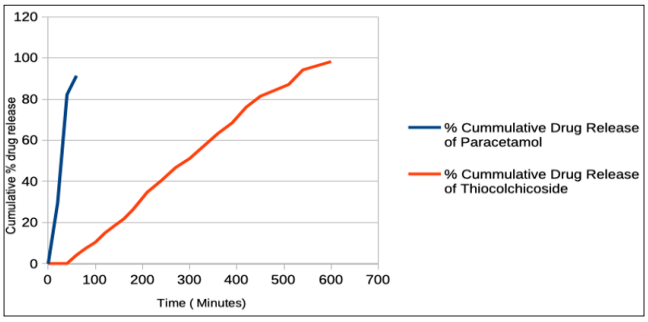

Figure 15: In- Vitro dissolution studies of bilayer tablet

A. Kinetic release modeling

The release profiles of an immediate release layer of all formulations were compared. The data were processed for regression analysis using MS-Excel statistical functions. The data were evaluated for zero-order, the first-order model Higuchi model, and Korsmeyers– Peppas model value shown in figure 16 & 17 . The data suggested that release kinetics of IR release layer follow zero-order drug release because the values of regression coefficient obtained (r2) is 0.957.

The release profiles of a sustained release layer of all formulations were compared with zero-order, first-order, Higuchi model, and Korsmeyers– Peppas model value shown in Figure 17. and regression coefficient value (r2) 0.991, 0.881, 0.900 and 0.916. Moreover, these formulations support the 'n' value is in the range 0.45–0.60 also having higher percentage cumulative drug release. The data suggested that release kinetics follow zero-order drug release because the values of regression coefficient obtained (r2) is 0.991 which is best fit model.

3.14 Parameters determined to analyze the mathematical model of dissolution of bilayer tablet

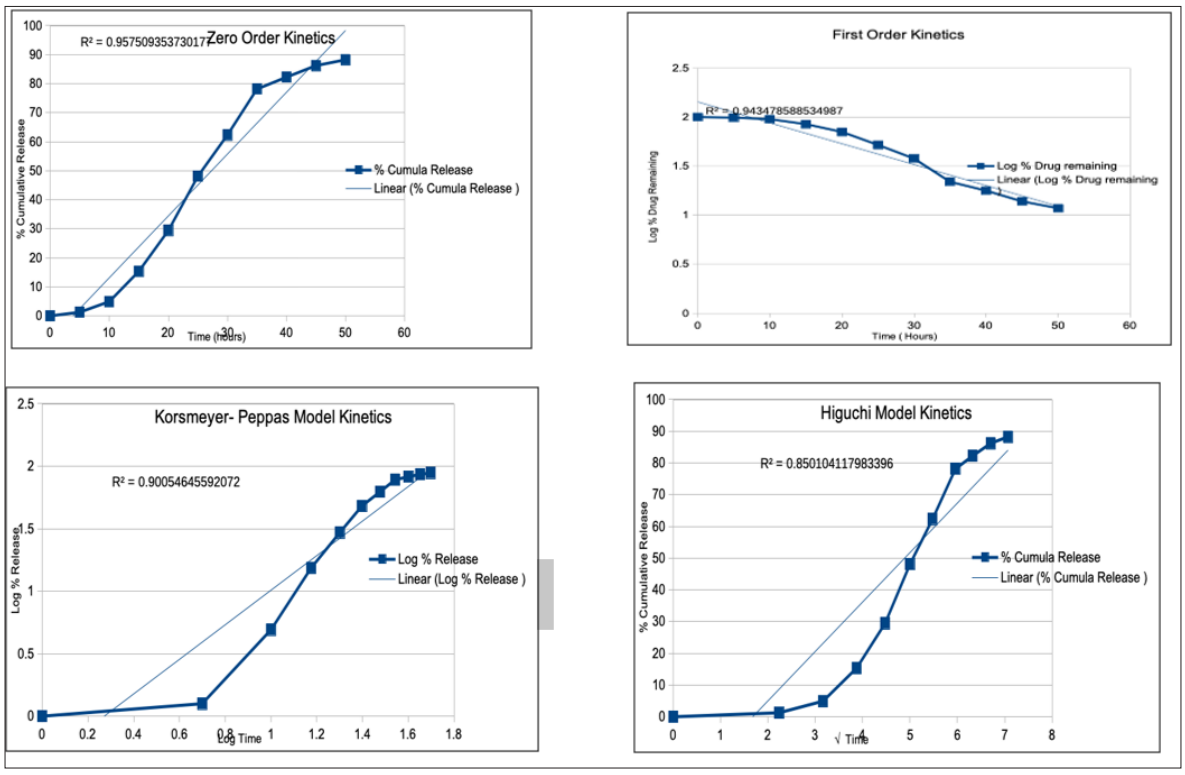

Figure 16: Dissolution model release kinetics for immediate release paracetamol

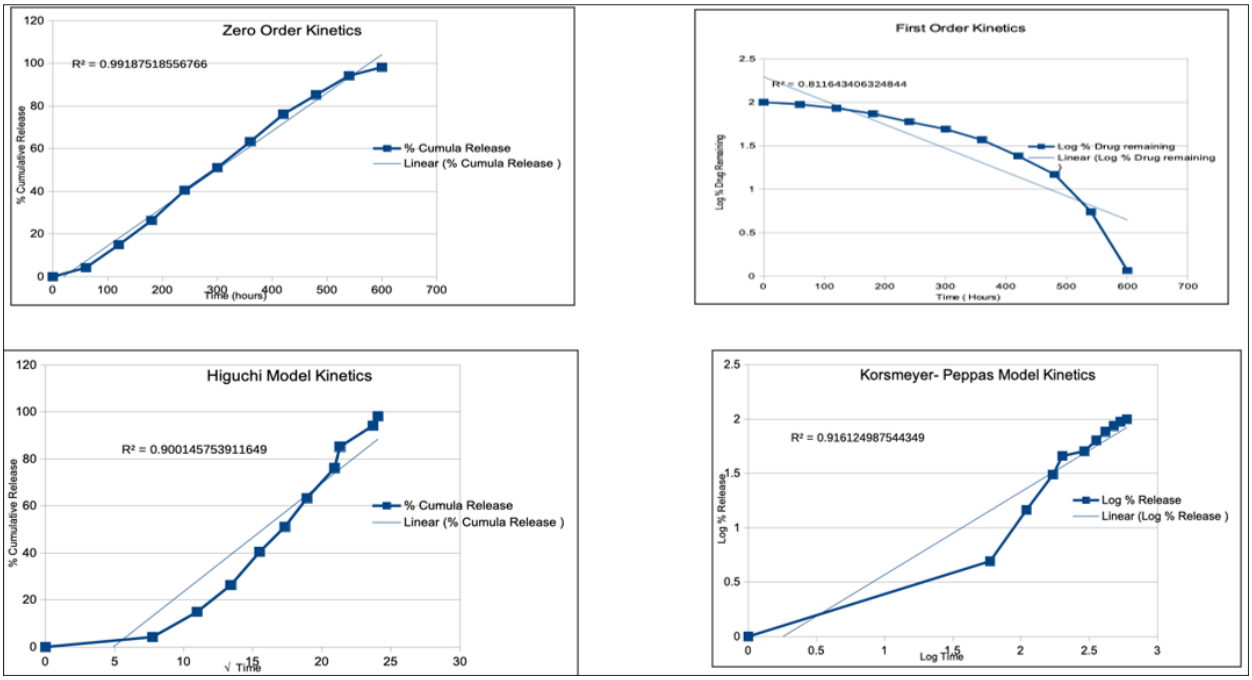

Figure 17: Dissolution release kinetics for sustained release thiocolchicoside

Table 11: Stability Test of the Bilayer Tablet

S. No.	Parameters	Results before stability study	Results after stability study
1.	Hardness	4.87	4.90
2.	Friability	0.45	0.42
3.	Weight Variation	670	670
4.	cummulative drug release (Paracetamol)	90.30	90.08
5.	cummulative drug release (Thiocolchicoside)	98.84	97.78

3.15 Stability test

For the purpose of the stability investigation, the optimised formulation was used. For the purpose of examining the stability of tablets, the storage conditions that were supplied were specifically 40°C±75% relative humidity (RH). The guidelines that were created with the conditions of the ICH. At regular intervals of two months, the tablets were examined and analysed for a variety of factors, including characteristics such as their hardness, disintegration, and pharmacological composition. Before the tablets were stored for stability tests, the results that were acquired were compared with those that were obtained via the examination of the tablet. As shown in table 11, The cumulative percent of drug released of the IR and SR layers did not exhibit any substantial changes. Similarly, friability, disintegration time, and weight variation remained unchanged. Therefore, it was determined that the formulation was stable.

4. Conclusion

IR and SR bilayer tablet formulation of paracetamol & thiocolchicoside was successfully prepared using BBD and used for optimization. The results suggested that the optimized formulation showed appropriate weight and hardness with sustained dissolution profiles in different pH conditions and better stability. Therefore, the optimized bilayer tablet of paracetamol & thiocolchicoside can be considered as a suitable substitute for the pain management.

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6. Conflict of Interest: None

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