Optimization of Drug Release Kinetics and Stability of a Chlordiazepoxide Hydrochloride-Clidinium Bromide Combination Capsule for the Treatment of Anxiety-Related GI Disorders

Kunal Kanojia, Pankaj Bhatt*, Sonal Mittal

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, 201206, India

pankajbhattb.pharma@gmail.com

ABSTRACT:

The goal of this research is to formulate and optimize an immediate-release capsule dosage form to control emotional and somatic factors in GI disorders. The prevalence of anxiety-related peptic ulcers and irritable bowel syndrome (IBS) is rising quickly in the current period, necessitating the urgent development of a novel combination to safely and effectively treat both conditions. In light of this, it was decided to combine two medications and formulate a capsule dosage form. The Chlordiazepoxide hydrochloride (benzodiazepines derivative) has limited aqueous solubility and dissolving rate in water, but it is highly soluble at lower pH levels or higher stomach pH levels. Because peptic ulcer patients have high stomach acid output, which facilitates medication solubility and absorption, this makes it an attractive treatment choice for these patients. The other medication in this combination, clidinium bromide (an anticholinergic agent) aids in lowering the secretions linked to disturbed mental health and lowers the motility of soft tissues in the GIT. Both medications appeared to work well together. The results of several trials with this combination showed how effective it might be in treating IBS and peptic ulcers linked to anxiety. Since sufficient research demonstrating the relationship between anxiety and ulcers is lacking, there are currently few therapy options available. Given that, this combination can reduce the majority of serious gastrointestinal problems and enhance the response. This research study serves as an example of how to design and create a unique, immediate-release capsule dosage form using an optimization-based methodology.

KEYWORDS: Chlordiazepoxide Hydrochloride, Clidinium Bromide, GI disorders, anxiety, Immediate release dosage form, optimization-based methodology

DOI: 10.48047/ecb/2022.11.12.94

INTRODUCTION:

Gastrointestinal (GI) disorders are a common health problem affecting millions of people worldwide. These disorders can be caused by a variety of factors, including emotional and somatic factors such as stress, anxiety, and depression[1]. Although several medications are available to treat GI disorders, they are not always effective in controlling emotional and somatic factors, which can exacerbate the symptoms of GI disorders[2]. Immediate-release capsule dosage forms have been widely used in the pharmaceutical industry due to their ease of administration and rapid onset of action. However, the development of an immediate-release capsule dosage form to control emotional and somatic factors in GI disorders presents a unique challenge. The formulation must not only effectively control the physical symptoms of GI disorders but also address the emotional and somatic factors that contribute to the symptoms[3].

The aim of this research paper is to formulate, evaluate, and optimize an immediate-release capsule dosage form to control emotional and somatic factors in GI disorders. The paper will present a detailed review of the literature on GI disorders and the various treatment options available, as well as an overview of immediate-release capsule dosage forms and their advantages in treating GI disorders[4]. The formulation of the immediate-release capsule dosage form will be based on an extensive literature review of active pharmaceutical ingredients (APIs) and excipients that are

effective in treating GI disorders and controlling emotional and somatic factors. The formulation will be evaluated for its physicochemical properties, such as particle size, flowability, and dissolution rate[5].
Optimization of the immediate-release capsule dosage form will be carried out using statistical tools such as the design of experiments (DoE) and response surface methodology (RSM)[6]. The optimized formulation will be further evaluated in vitro and in vivo to assess its efficacy and safety in controlling emotional and somatic factors in GI disorders[7].
The results of this research paper will provide valuable insights into the development of an immediate-release capsule dosage form for the treatment of GI disorders that addresses emotional and somatic factors. This could potentially lead to the development of a more effective and patient-friendly treatment option for individuals suffering from GI disorders.

MATERIALS AND METHOD:

Materials

Chlordiazepoxide hydrochloride was received as a gift sample from Hetero laboratories in Hyderabad. Clidinium bromide was purchased from local suppliers Corn starch, talc, and sorbitol are the excipients used in this study which were used as an analytical grade available in college research facilities.

Method:

Identification of both active pharmaceutical ingredients using the IR Spectroscopy method

The FT-IR spectrophotometer was used to develop the FT-IR spectrum. The infrared spectrum was taken for the pure drugs i.e. – chlordiazepoxide hydrochloride and clidinium bromide. FTIR was carried out by the KBr disk method using computer-mediated Fourier-transform infrared spectroscopy (FTIR). The drug-KBr ratio was taken, and the mixture was subjected to 10 tonnes of pressure in a hydraulic press to create a pellet. The produced pellet was placed within samples and kept there while the devices recorded the IR peaks[8]. The acquired IR spectra were contrasted with the FT-IR spectrophotometer that is used to develop the FT-IR spectrum. The infrared spectrum was taken for the pure drugs, i.e., chlordiazepoxide hydrochloride and clidinium bromide. FTIR was carried out by the KBr disk method using computer-mediated Fourier transform infrared spectroscopy (FTIR). typical IR drug spectrum. The produced pellet was placed within samples and kept there while the devices recorded the IR peaks. The acquired IR spectra have been contrasted with the typical IR drug spectrum[9].

Study of physicochemical properties of both Active Pharmaceutical Ingredients:

Pre-formulation studies

Pre-formulation is a body of research that examines a novel drug candidate's physicochemical properties and how they could affect dosage form development and drug performance. This might be useful for creating new products or demonstrating the necessity of molecular change. Before developing a pharmaceutical formulation, consideration must be given to the inherent chemical and physical characteristics of each medicine. This characteristic lays the groundwork for producing dosage forms by combining drugs with medicinal components[10].

Appearance

The evaluation of physical appearance is one of the most important drug tests. The color may reveal signs of impurity or pollution[11]. The physical appearance of both drug substances is tabulated in Table 1.

Melting point

A substance's melting point is often defined as the temperature at which it changes from a solid to a liquid. The temperature at which a liquid under atmospheric pressure changes from a solid to a liquid is known as its melting point. The melting point of a liquid at atmospheric pressure is the temperature at which it transforms from a solid to a liquid. At this point, the liquid and solid phases are in equilibrium. The melting points of drug compounds are determined by the melting point instrument[12]. The melting point of both drug substances is mentioned in Table 1.

Procedure (by Capillary tube method)
The use of a capillary tube. A burner was used to screen the capillary tube, and after that, the capillary pipe was expanded with both ends grabbing it and pressing in opposing directions to screen it on one end. A little amount of telmisartan has been put on a sterile surface. The capillary tube has been filled with the substance. On the melting point unit, a capillary tube (Veego/Macro Scientific Works) is placed. As the sample started to melt, its temperature was continuously monitored and calculated using a thermometer. For the most trustworthy outcomes, gradual heating was adopted. It was noted that the sample begins to fuse and eventually completes the fusion.

Solubility studies
A small quantity of the drug sample was taken in a test tube, and the solubility was determined by dissolving the drug in 1 ml of various solvents[13-14]. The solubility of both drug substances is mentioned in Table 1.

Particle size
PSD and shape have an impact on a drug's chemical and physical characteristics. It is commonly accepted that poorly soluble drugs are more accessible when given as a finely divided powder as opposed to a coarse substance during the rate-limiting phase of the absorption process. The flow, the size of the powder and granules, and the efficiency of their mixing are all impacted by the tablet's shape and size. The Malvern method is used to calculate the drug's particle size distribution (PSD)[15]. The details of the particle size distribution for both drug substances are described in Table 2.

Bulk density and Tapped density

For measuring the bulk density and tapped density, a few grams of powder are added to a 100 ml measuring cylinder and lightly agitated to dislodge any agglomerates that may have developed. The bulk density is then calculated. Following the initial volume measurement, the cylinder was set to fall independently onto a hard surface from a height of 2.5 cm every 2 seconds until no more volume changes were observed, at which point the tapping was stopped. The following formulas were used to determine BD and TD:
BD = weight of the powder/volume of the packing

TD = weight of the powder / tapped volume of the packing[16].

Hygroscopicity
As a function of humidity, a material's hygroscopicity (ability to absorb or release water) is measured (i.e., water activity) A moisture sorption isotherm that plots the changing water content against temperature and RH would be the best technique to measure hygroscopicity[17]. The details of APIs hygroscopicity are mentioned in Table 3.

Drug-Excipient compatibility studies:

Drug excipient compatibility was performed for physical observation and chemical evaluation for impurities through analysis of a binary mixture (with a single API and with the combination of both APIs) stored at 40°C/75% RH in open glass vials for four weeks. The excipient compatibility studies assessed common excipients acting as fillers, disintegrants, and glidants[18]. The binary mixture-physical observation investigation on drug excipient compatibility is summarized in Table 4.

Optimization of formulation:

Drug substance particle size selection for product development

The larger particle size of the pharmaceutical ingredient improves flow and increases its manufacturing potential. The physical and flow characteristics of drug substances A and B were assessed, and the results are described. However, for those highly soluble medications, the particle size has little impact on in vivo performance. The impact of drug product particle size on the homogeneity of content parameters is summarized in Table 5.

Optimization for the impact of sorbitol to corn starch ratio

The main goal of this is to choose an appropriate sorbitol-to-starch ratio in order to determine whether it affects the CQA of the medicinal product. By using the reverse engineering method on RLD, the ratio was discovered. Assigning values of 3:1 and 7:1 correspondingly, the sorbitol/corn starch ratio is changed into a continuous numeric variable as a proportion of sorbitol and corn starch in a dual filler combination. This trial study's main objective is to understand the physical and chemical effects of the sorbitol/ corn starch ratio on the drug product CQA. The result is summarized in Table 6.

Optimization for corn starch selection

Different grades of maize starch were used in development studies. Different moisture limitations, namely 14 percent and 4 percent, were applied for the grades. The composition information for development batches is displayed in Table 7.

Sieve selection and sifting of API

The first phase in the direct blending and mixing production process, which might affect the capsule assay and content uniformity, is the proper sieve selection. The desired batches were made, and the sieve's impact was examined and mentioned in Table 8.

Pre-lubrication and lubrication process development

Pre-lubrication and lubrication stage blend uniformity data have been shown in Tables 9, and 10, respectively, wherein the blending time has been optimized with a fixed blender speed.

Manufacturing process selection:

Manufacturing techniques such as direct mixing and blending were chosen. The aforementioned technique was used to prepare batches, and the resulting information was collated. Two methods of batch preparation, namely direct mixing and blending and direct mixing and blending with milling, were used to optimize the milling process.

Milling can be defined as the process in which we use a milling machine with rotatory cutters. It involves the application of the physical and mechanical breakdown of coarser particles into fine particles.

Procedure involved

Weigh all the ingredients accurately. Sift sorbitol Part-I, II, III, IV, and V through sieve no. #60 and collect the material into a double polybag. Pass the sifted sorbitol part-I through the Quadro co-mill using an 18R screen. Co-sift manually both the APIs, corn starch, and sorbitol part-I from step 3 to sieve #60. Co-sift step 4 ingredients along with sorbitol part II through sieve #60. Co-sift step 5 ingredients along with sorbitol part-III through sieve #60. Pass the material of step 6 to the Quadro co-mill twice using an 18R screen at a slow speed and collect all the material into a double-lined polybag. Pass the sorbitol part-IV through Quadro co-mill using an 18R screen at low speed. Load the material from step-7 and 8 into a suitable conta blender and perform the pre-lubrication and lubrication stages. Pass the sorbitol part-V from Quadro co-mill using an 18R screen at a slow speed. Co-shift the material obtained from step 10 and add talc then pass it through sieve #60. Transfer the obtained material from 11 to the blender i.e., step 9, and blend it for 15 min and 8 rpm. After completion of the pre-lubrication and lubrication stages unload the blender and collect the material in a poly bag. Finally, fill the capsule of the required quantity by using a manual capsule-filling machine.

Note- The whole process was carried out under a sodium vapor lamp at RH lower than 40% in the pilot-bio area as one of the drugs is moisture and light-sensitive.

In-vitro studies:

The dissolving was conducted for the innovator as well as for a variety of experimental studies. The findings are displayed below in a variety of ways. For the dissolution study, 900 ml of water has been used as dissolution media in USP-I (Basket type) apparatus at 100 rpm till the complete dissolution of the finished product took place. The solubility data of the finished product for trials 3 and 4 is described in Table 11, in which comparative dissolution data of both drug substances are given individually in Figures 3 and 4.

Stability studies:

Stability studies were performed as per the ICH guidelines. Selected formulations of the final capsule dosage form were packed in an HDPE container and stored at (40 ± 2 °C / 75 ± 5 % R.H), for a period of 3 months. Samples from each formulation that were kept for examination were withdrawn at definite intervals. The withdrawn samples were evaluated for assay, water by KF, percentage drug release, and impurity detection. The results of stability studies were summarized in Tables 12, 13, and 14.

Stability testing's main objective is to collect verifiable data on how the quality of an API or final product varies over time and in reaction to various variables including temperature, light, and humidity. For the final product, stability studies were conducted which have been summarized.

RESULT AND DISCUSSION:

Identification of both active pharmaceutical ingredients using the FTIR spectroscopy method

FTIR spectroscopy is used for the identification of both APIs, which are available in pure form. Figures 1 and 2 contain the FTIR spectra of chlordiazepoxide hydrochloride and clidinium bromide, respectively. According to observation, no significant changes have been seen in the fingerprint region and both drug substances are identified as being used in the formulation.

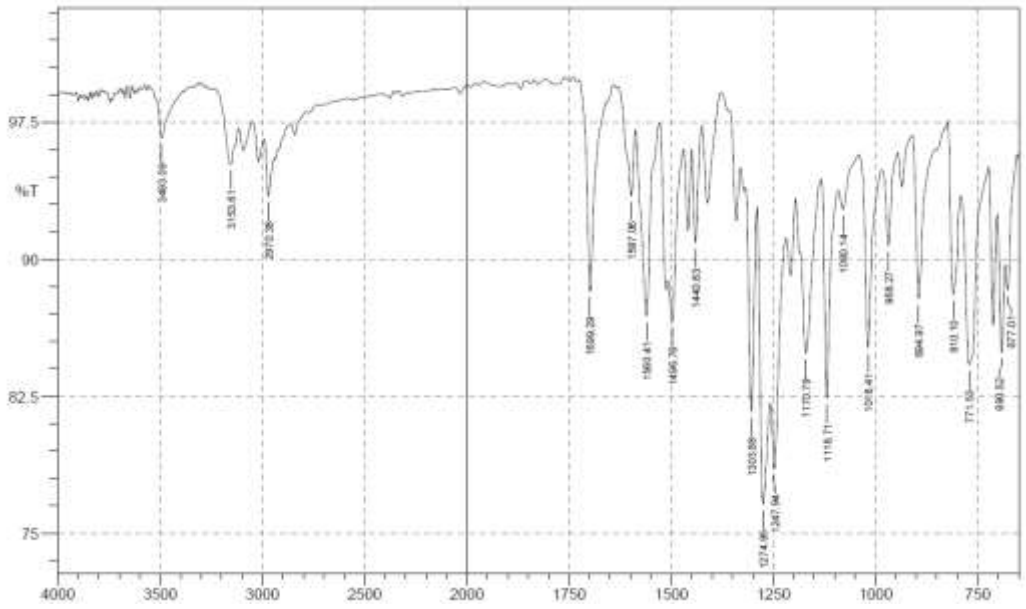


Figure 1. FTIR spectra of chlordiazepoxide hydrochloride

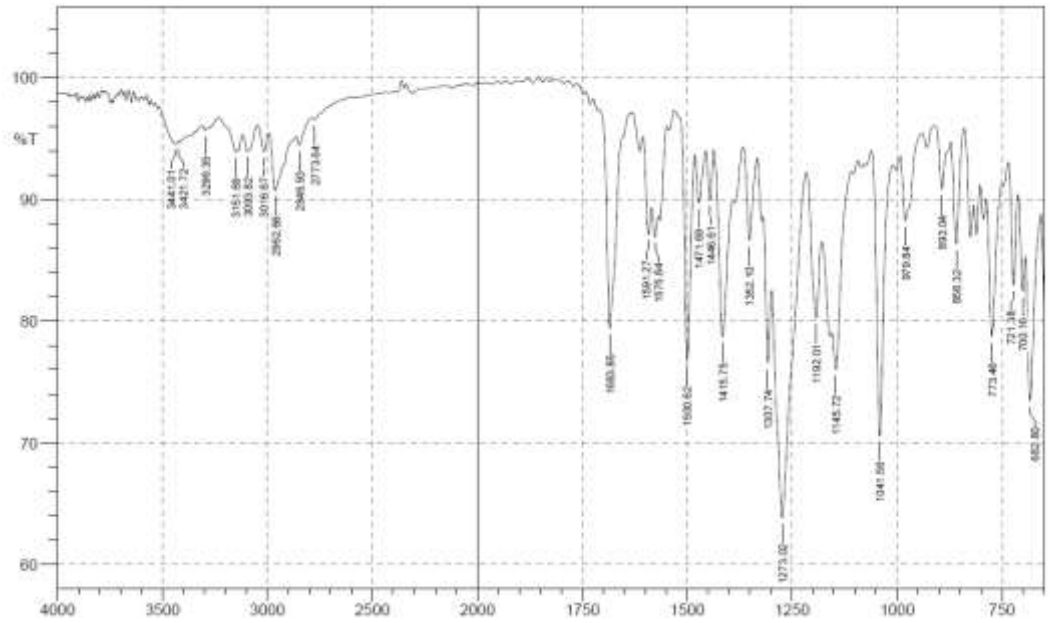


Figure 2. FTIR spectra of Clidinium bromide

Pre-formulation studies:

Appearance

The benzodiazepine derivative drug A is white to slightly yellow crystalline yellow powder whereas the anticholinergic drug B is white crystalline powder.

Melting point

The melting point apparatus is used to calculate the melting points of drugs A and B, and the results are provided in tabular form in Table 1.

Solubility studies

The solubility of the drug substances has been studied in various organic and inorganic solvents. The results of solubility are described below in Table 1.

Table 1. Physical Appearance, Melting point & Solubility of drug substances

Sr. No.	Drug	Physical Appearance	Melting Point	Solubility
1	Chlordiazepoxide Hydrochloride	White to slightly yellow crystalline yellow powder.	Approx. 210°C	Freely soluble in water, sparingly soluble in ethanol, insoluble in hexane
2	Clidinium Bromide	White crystalline powder	220 °C	Soluble in methanol, water, and ethanol, slightly soluble in benzene.

Particle size distribution

The particle size distribution of both active pharmaceutical ingredients using the Malvern technique is mentioned below in Table 2.

Table 2. PSD details of drug substances

Particle size distribution	Chlordiazepoxide Hydrochloride	Clidinium Bromide
D10	3.51 µ	13.225 µ
D50	13.4 µ	33.669 µ
D90	42.4 µ	97.725 µ

Density

The density of chlordiazepoxide hydrochloride and clidinium bromide was found to be 0.37gm/ml & 0.43 gm/ml respectively.

Hygroscopicity

In order to assess the hygroscopic nature of API, it provides a measurement of the sample's capacity to absorb and release water when both the APIs are exposed to the environment. The hygroscopicity of both drugs is mentioned in Table 3.

Table 3. Hygroscopicity of Drug substances

Sr. No.	Drug	Result of The Determination
1	API A	Non-Hygroscopic
2	API B	Non-Hygroscopic

Drug-excipient compatibility studies:

Based on the physical observation data of binary mixtures with individual and combination of APIs, we can conclude that the selected excipients can be used in the formulation because no compatibility issue was observed with studied excipients. The results of compatibility studies were mentioned below in Table 4.

Table 4. Drug excipient compatibility study, binary mixture- physical observation

Trial No. Trial 1A			
Binary mixture	**Ratio**	**Initial**	**Open, 40 ˚C/75% RH (1 M)**
API A	NA	Off-white granular powder	No change in color, with free following powder
API B	NA	Off-white granular powder	No change in color, with free following powder
API A: API B	1:0.5	Off-white granular powder	No change in color, with free following powder
API A: sorbitol	1:10	Off-white granular powder	No change in color, with free following powder
API B: sorbitol	1:10	Off-white granular powder	No change in color, with free following powder
API A + API B: sorbitol	1:10	Off-white granular powder	No change in color, with free following powder

API B: Corn starch	1:10	Off-white granular powder	No change in color, with free following powder
API A: Corn starch	1:5	Off-white granular powder	No change in color, with free following powder
API A + API B: Corn starch	1:5	Off-white granular powder	No change in color, with free following powder
API B: Talc	1:2	Off-white granular powder	No change in color, with free following powder
API A: Talc	1:1	Off-white granular powder	No change in color, with free following powder
API A + API B: Talc	1:1	Off-white granular powder	No change in color, with free following powder
API B: hard gelatin capsule	1:2	Off-white granular powder with off-white hard gelatin size' 3'capsule	No change in the color of the API and empty shell capsule
API A: hard gelatin capsule	1:1	Off-white granular powder with off-white hard gelatin size' 3'capsule	No change in the color of the API and empty shell capsule
API A + API B: hard gelatin capsule	1:0.67	Off-white granular powder with off-white hard gelatin size' 3'capsule	No change in the color of the API and empty shell capsule

Optimization of formulation:

Drug substance particle size selection for product development

Table 5. Proposed PSD limits for drug substances

S. No.	API	PSD details		
		D90 (µ)	**D50 (µ)**	**D10 (µ)**
1	API A	NMT 80 µ	NMT 30 µ	NMT 10 µ
2	API B	NMT 250 µ	NMT 70 µ	NMT 25 µ

***NMT-** Not more than.

Optimization for the impact of sorbitol to corn starch ratio

For the optimization of formulation, the ratio of sorbitol/ corn starch along with API and remaining excipient was filled in the capsules. The blend is filled in the capsule and the finished capsule parameters are determined. No significant difference was observed w.r.t blend properties and capsule fill weight.

Table 6. Parameter of filled capsules along with blend properties of both trials.

Trial No.	**Trial 3**	**Trial 4**
Sorbitol/ corn starch ratio	7:1	3:1
Individual weight (mg)	250-258	248-257
Lock length (mm)	15.47-15.64	15.49-15.70
Disintegration time	08 Min 10 sec	09 Min 50 sec
Trial No.	**Trial 3**	**Trial 4**
Bulk density (g/ml)	0.666	0.681
Tapped density	0.882	0.909
CI	24.444	25.000
HR	1.323	1.333

Optimization for corn starch selection

After optimization of the sorbitol: corn starch ratio, the batches are prepared and loaded into the stability at 40˚C / 75% RH for three months, and the data were compared with the initial one. As evident, there is a significant increase in API-related compound A impurity in the batch having higher moisture content than that with low moisture content. It is proposed that corn starch with low moisture content will be used to develop other batches.

Table 7. Stability data of batches with different corn starch

Batch No.	**X**		**Y**	
Pack details	**HDPE 120CC NW**		**HDPE 120CC NW**	
Corn starch	**14% moisture**		**4% moisture**	
Condition	**Initial**	**40^0/ 75% RH**	**Initial**	**40^0/ 75% RH**
Related substances				
API-related compound A	0.230	2.20	0.88	0.771
2 amino 5 chloro-benzophenone	0.00	0.00	0.00	0.00
API-related compound A	0.00	0.00	0.00	0.00
Highest unknown impurity	0.00	0.00	0.00	0.00
Total impurity	0.230	2.20	0.88	0.771

Sieve selection and sifting of API

The effect of sieve selection and sifting on API/RM on the drug product is studied by determining the blend assay and content uniformity. However, the content uniformity and blend assay were meeting the specification, and considering the low concentration of API and PSD of excipients used #ASTM 60 is preferred.

Table 8. Effect of sieve selection and sifting of API/RM on drug product content uniformity and assay.

Trial No.	**Trial 5**	**Trial 6**	**Trial 5**	**Trial 6**
API Name	**Drug A**		**Drug B**	
CU-1	99.0	97.1	99.5	97.6
CU-2	100.0	97.6	99.4	98.6
CU-3	101.3	99.7	104.2	100.8
CU-4	101.9	101.5	101.6	100.8
CU-5	99.7	100.6	99.2	101.1
CU-6	102.1	97.1	105.0	97.4
CU-7	101.5	98.3	103.1	98.4
CU-8	102.7	97.2	108.1	97.3
CU-9	99.3	96.2	98.4	97.0
CU-10	95.8	97.7	98.6	97.0
Mean	**100.3**	**98.3**	**101.7**	**98.6**
SD	2.04	1.7	3.28	1.7
RSD	2.03	1.8	3.23	1.7
Min	95.8	96.2	98.4	97.0
Max	102.7	101.5	108.1	101.1

Pre-lubrication and lubrication process development

Table 9. Blend uniformity data Pre-lubrication stage

Stage	**Pre-lubrication (15 min)**		**Pre-lubrication (30 min)**		**Pre-lubrication (45 min)**	
API	**Drug A**	**Drug B**	**Drug A**	**Drug B**	**Drug A**	**Drug B**
TR-1	97.3	98.1	100.1	102.1	98.3	99.0
TL-2	98.8	100.1	100.6	100.4	98.1	98.6
TF-3	98.0	98.8	99.8	100.8	99.5	98.8
TB-4	98.6	101.6	100.6	100.0	98.6	99.7
MR-5	97.3	98	99.9	99.5	97.3	98.2
ML-6	98.0	99.5	97.8	97.9	96.8	99.2
BR-7	97.7	98.9	99.4	98.4	98.6	98.3
BL-8	98.4	98.9	100.6	98.9	98.8	98.9
BF-9	98.4	99.5	98.9	98.6	98.5	97.8
BB-10	98.8	99.6	100.2	102.6	98.7	99.0
Mean	**98.1**	**99.3**	**99.8**	**99.9**	**98.3**	**98.8**
SD	0.6	1.0	0.9	1.6	0.8	0.6
RSD	0.6	1.1	0.9	1.6	0.8	0.6
Min	97.3	98.0	97.8	97.9	96.8	97.8
Max	98.8	101.6	100.6	102.6	99.5	99.7
Assay	**99.1**	**100.2**	**99.7**	**99.8**	**99.8**	**99.7**

Table 10. Blend uniformity data at lubricated blend stage B. No. Y and Z

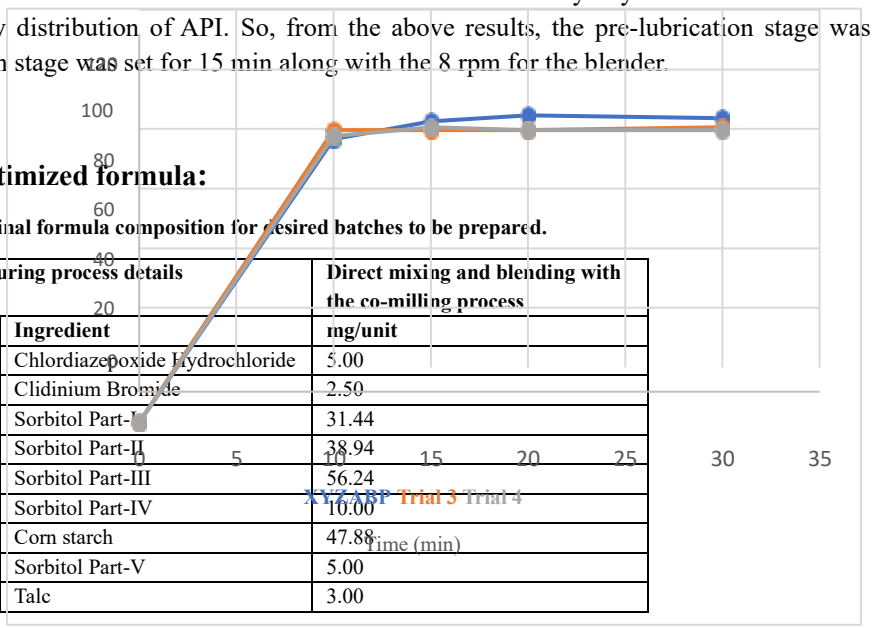
Batch No.	**Y**		**Z**			
Stage	**Lubricated blend- 05 min**		**Lubricated blend- 10 min**		**Lubricated blend- 15 min**	
API name	**API A**	**API B**	**API A**	**API B**	**API A**	**API B**
TR-1	97.5	98	98.1	101.2	97.7	99.4
TL-2	96.5	96.9	97.4	99.9	96.8	99.3
TF-3	97.3	98.4	97.0	99.1	97.6	99.7
TB-4	97	98	96.3	96.8	96.6	99.9
MR-5	96.1	97.4	96.8	98.0	96.5	97.3
ML-6	97.4	97.6	96.7	100.6	97.0	98.9
BR-7	96.4	96.4	96.4	100.1	96.1	96.5
BL-8	96.6	99	97.1	99.0	96.7	98.2
BF-9	97.5	100.7	97.5	97.8	97.5	99.6
BB-10	97.5	97.8	96.7	97.4	97.6	97.7
Mean	**97**	**98**	**97.0**	**99.0**	**97.0**	**98.7**
SD	0.5	1.2	0.6	1.5	0.6	1.2
RSD	0.6	1.2	0.6	1.5	0.6	1.2
Min	96.1	96.4	96.3	96.8	96.1	96.5
Max	97.5	100.7	98.1	101.2	97.7	99.9
Assay	**99.6**	**98.4**	**97.6**	**98.4**	**97.0**	**98.6**

Inference - From the above-summarized data we can clearly say that the duration of blending influences the uniformity distribution of API. So, from the above results, the pre-lubrication stage was set for 45 min, and the lubrication stage was set for 15 min along with the 8 rpm for the blender.

Final optimized formula:

Table 11. Final formula composition for desired batches to be prepared.

Manufacturing process details		**Direct mixing and blending with the co-milling process**
S. No.	**Ingredient**	**mg/unit**
1	Chlordiazepoxide Hydrochloride	5.00
2	Clidinium Bromide	2.50
3	Sorbitol Part-I	31.44
4	Sorbitol Part-II	38.94
5	Sorbitol Part-III	56.24
6	Sorbitol Part-IV	10.00
7	Corn starch	47.88
8	Sorbitol Part-V	5.00
9	Talc	3.00



In-vitro studies:

The release profile of the formulation is mentioned below in Table 14 and according to USP acceptance criteria, a dissolution rate of NLT 75% in 30 min in water was set as the target for pharmaceutical development studies. The dissolution profile of trial batches 3 & 4 was compared with the reference product to meet the pharmaceutical specifications of in-vitro studies.

Table 12. Comparison of dissolution profile between reference and test product

Water / 900 ml / USP Apparatus 1 / 100 RPM						
Time (Min)	**Drug A dissolved**			**Drug B dissolved**		
	Batch No.					
	Drug A	**Trial 3**	**Trial 4**	**Drug B**	**Trial 3**	**Trial 4**
0	0	0	0	0	0	0
10	88	98	95	95	98	96
15	99	100	99	101	98	99
20	102	100	99	103	98	98
30	102	100	99	102	99	98

Figure 3. Comparative dissolution of Reference and Test product in water (Drug-A)

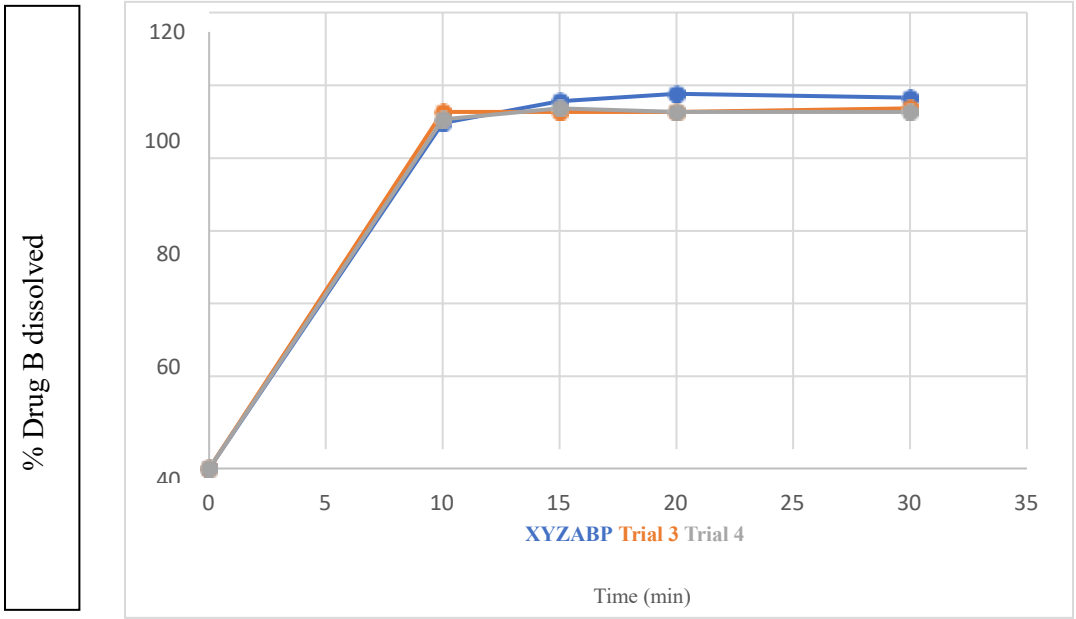


Figure 4. Comparative dissolution of Reference and Test product in water (Drug-B)

Stability studies:

A pharmaceutical drug product may experience a variety of changes while being stored, including those that affect its appearance, consistency, content uniformity, clarity (in terms of solution), moisture content variation, particle size, and shape, pH, and package integrity. These changes can all have an impact on the stability of the drug product. So, we must verify the final completed product's stability to make sure that no such alteration has occurred in the formulation. The finished product is stored at (40 ± 2 °C / 75 ± 5 % R.H), for a period of 3 months. Samples from each formulation that were kept for examination were withdrawn at definite intervals. The withdrawn samples were evaluated for assay, water by KF, percentage drug release, and impurity detection. The results of stability studies are summarized in Tables 15, 16 & 17.

For accelerated condition- 40 ± 2° C/ 75 ± 5% RH

Table 13. Detection of Assay and Water by KF of final optimized product at 40 ± 2° C/ 75 ± 5% RH

Trial X
Pack- HDPE

Condition- 40 ± 2° C/ 75 ± 5% RH			
Specification	**Assay**		**Water by KF**
	API B	**API A**	
	90.0%-110.0%		**NMT 10%**
Initial	99.2	99.2	5.36
1 month	98.4	99.3	5.89
3 months	98.1	97.3	5.24

Table 14. Percentage Drug release of final optimized product at 40 ± 2° C/ 75 ± 5% RH

Trial 10																
Pack- HDPE																
Condition- 40 ± 2° C/ 75 ± 5% RH																
Specification	**% Drug release of API B**								**% Drug release of API A**							
	5	**10**	**15**	**20**	**30**	**45**	**60**	**Infinity**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**Infinity**
Initial	52	101	101	101	102	102	102	101	49	98	101	100	102	103	102	101
1 month	68	97	100	100	99	99	99	98	65	90	94	90	94	97	102	101
3 months	NR	97	103	103	101	NR	NR	103	48	86	93	95	95	NR	NR	96

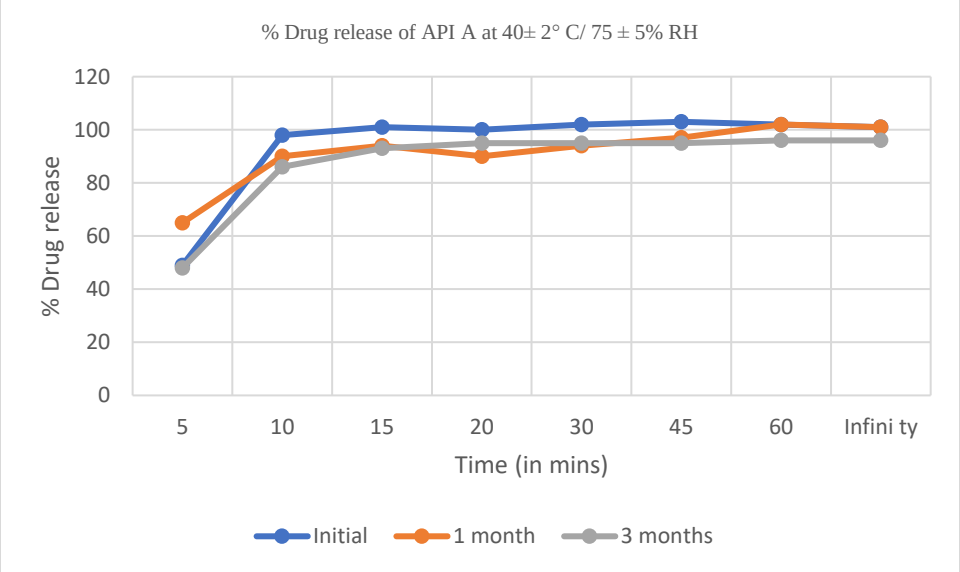


Figure 5. % Drug release of API A at 40 ± 2° C/ 75 ± 5% RH

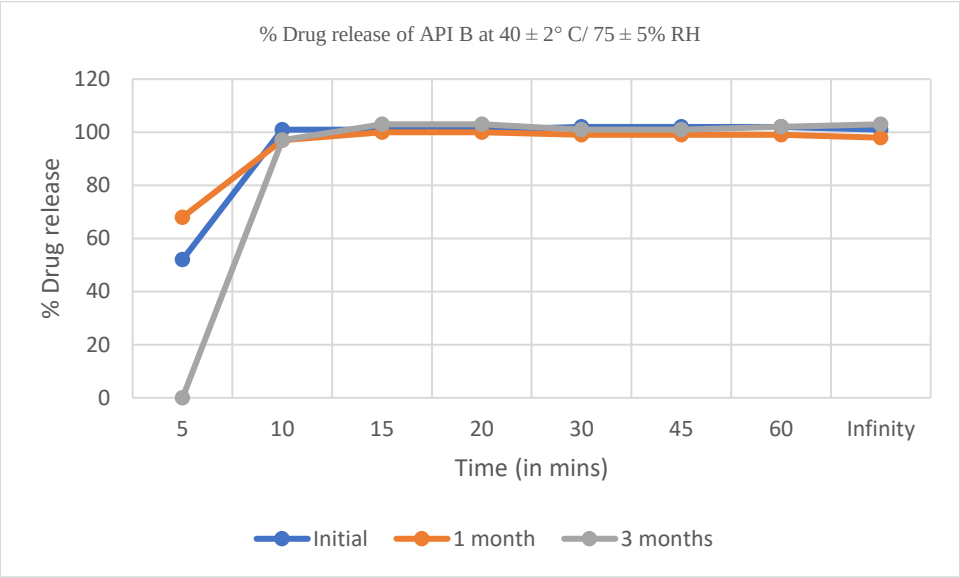


Figure 6. % Drug release of API B at 40 ± 2° C/ 75 ± 5% RH

Table 15. Impurities detection of final optimized product at 40 ± 2° C/ 75 ± 5% RH

Condition- 40° C ± 2°C/ 75 ± 5% RH							
Related substances	**Impurities related to API- A**			**Impurities related to API- B**	**Total impurity**	**Related compound impurityby TLC**	
	API- A related comp. A	**Impurity - B**	**Impurity -C**	**Impurity- D**	**Impurity -E**		
Limits	**NMT- 3.0**		**NMT- 0.1**	**NMT- 0.5**	**NMT-5.0**	**NMT- 1.0**	
Initial	0.033	ND	ND	ND	ND	0.033	ND
1 month	0.435	ND	ND	ND	ND	0.435	ND
3 Months	1.234	ND	ND	ND	ND	1.234	ND

Inference – Based on the aforementioned stability at accelerated stability study, the final optimized formulation exhibits no sort of appreciable change in physical appearance or dissolution; no impurity detection; no significant change in assay and water by KF. Hence, it should be concluded that the final optimized product is stable, safe, and effective.

CONCLUSION:

The study mentioned above leads to the conclusion that the medications we use to treat anxiety, peptic ulcers, and IBS are compatible with one another, and optimization studies linked to them show they have a significant amount of therapeutic potential for treating anxiety associated GI- disorders like peptic ulcers, and IBS. The physicochemical characterization and bioequivalence experiments show that the new capsule dosage form satisfies all pharmaceutical requirements.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGMENT:

We are highly grateful to the Director Dr. (Col.) A. Garg and Joint Director, Dr. Manoj Goel, KIET Group of Institutions, and Dr. K. Nagarajan, Principal, KIET School of Pharmacy, Ghaziabad for their motivation, and all-round support.

ABBREVIATIONS:

GI- Gastrointestinal, IBS- Irritable Bowel Syndrome, API- Active Pharmaceutical Ingredient, RSM- Response-Surface Methodology, DoE- Design of Experiments, FTIR- Fourier Transform Infrared, KBr- Potassium Bromide, PSD- Particle Size Distribution, BD- Bulk Density, TD- Tapped Density, KF- Karl Fischer, SD- Standard Deviation, RSD- Relative Standard Deviation, NMT- Not More than, NLT- Not Less than, CQA- Critical Quality Attributes, RLD- Reference Listed Drug, ICH- International Council of Harmonization, HDPE- High-Density Poly-Ethylene, RH- Relative Humidity.

REFERENCES:

[1] Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry [Internet]. 2001 [cited 2023 Jun 13];62 Suppl 8:28–36; discussion 37. Available from: https://www.psychiatrist.com/read-pdf/4153/

[2] Keefer L, Palsson OS, Pandolfino JE. Best practice update: Incorporating psychogastroenterology into management of digestive disorders. Gastroenterology [Internet]. 2018;154(5):1249–57. Available from: http://dx.doi.org/10.1053/j.gastro.2018.01.045

[3] S. Singh, B. Pankaj, K. Nagarajan, N. P. Singh, and V. Bala, "Blockchain with cloud for handling healthcare data: A privacy-friendly platform," Mater. Today, vol. 62, pp. 5021–5026, 2022.

[4] Thiwan SIM, Drossman DA. Treatment of functional GI disorders with psychotropic medicines: A review of evidence with a practical approach. Gastroenterol Hepatol (N Y). 2006;2(9):678–88.

[5] Pharmatutor.org. [cited 2023 Jun 13]. Available from: https://www.pharmatutor.org/articles/review-immediate-release-drug-delivery-systems.

[6] P. Bhatt, S. Singh, S. Kumar Sharma, and S. Rabiu, "Development and characterization of fast dissolving buccal strip of frovatriptan succinate monoydrate for buccal delivery," Int. J. Pharm. Investig., vol. 11, no. 1, pp. 69–75, 2021.

[7] Nyol S, Gupta MM. Immediate drug release dosage form: A review. J Drug Deliv Ther [Internet]. 2013;3(2). Available from: http://dx.doi.org/10.22270/jddt.v3i2.457

[8] S. Singh, P. Bhatt, N. Alfuraiji, M. M. Thuwaini, and A. E. Snafi, "Cardiovascular comorbidity of COVID-19 disease: A review," WJPMR, vol. 8, no. 4, pp. 216–225, 2022.

[9] Iskandarani B, Clair JH, Patel P, Shiromani PK, Dempski RE. Simultaneous optimization of capsule and tablet formulation using response surface methodology. Drug Dev Ind Pharm [Internet]. 1993;19(16):2089–101. Available from: http://dx.doi.org/10.3109/03639049309069343

[10] M. K. Malik et al., "Significance of chemically derivatized starch as drug carrier in developing novel drug delivery devices," Nat. Prod. J., vol. 12, 2022.

[11] Tarasiuk A, Mosińska P, Fichna J. Triphala: current applications and new perspectives on the treatment of functional gastrointestinal disorders. Chin Med [Internet]. 2018;13(1). Available from: http://dx.doi.org/10.1186/s13020-018-0197-6

[12] Pankaj, "Cyclodextrin modified block polymer for oral chemotherapy," J. Pharm. Res. Int., pp. 21–29, 2021.

[13] Lawson G, Ogwu J, Tanna S. Quantitative screening of the pharmaceutical ingredient for the rapid identification of substandard and falsified medicines using reflectance infrared spectroscopy. PLoS One [Internet]. 2018;13(8):e0202059. Available from: http://dx.doi.org/10.1371/journal.pone.0202059

[14] S. Singh, S. Kumar Sharma, P. Mehrotra, P. Bhatt, and M. Kaurav, "Blockchain technology for efficient data management in healthcare system: Opportunity, challenges and future perspectives," Mater. Today, vol. 62, pp. 5042–5046, 2022.

[15] Pharmaceuticalonline.com. [cited 2023 Jun 13]. Available from: https://www.pharmaceuticalonline.com/doc/characterization-and-mapping-of-active-pharma-0002.
[16] M. K. Malik, P. Bhatt, J. Singh, R. D. Kaushik, G. Sharma, and V. Kumar, "Preclinical safety assessment of chemically cross-linked modified mandua starch: Acute and sub-acute oral toxicity studies in Swiss albino mice," ACS Omega, vol. 7, no. 40, pp. 35506–35514, 2022.

[17] Streng WH. Physical chemical characterization of drug substances. Drug Discov Today [Internet]. 1997;2(10):415–26. Available from: http://dx.doi.org/10.1016/s1359-6446(97)01077-5
[18] S. Singh, P. Bhatt, S. K. Sharma, and S. Rabiu, "Digital Transformation in Healthcare: Innovation and Technologies," in Blockchain for Healthcare Systems, Boca Raton: CRC Press, 2021, pp. 61–79.

[19] Pharmaceuticalonline.com. [cited 2023 Jun 13]. Available from: https://www.pharmaceuticalonline.com/doc/physical-appearance-determination-of-a-drug-substance-utilizing-a-commercially-available-color-guide-0001.
[20] P. Bhatt, S. Singh, S. K. Sharma, and V. Kumar, "Blockchain technology applications for improving quality of electronic healthcare system," in Blockchain for Healthcare Systems, Boca Raton: CRC Press, 2021, pp. 97–113.

[21] Usp31nf26s1_c741, general chapters: MELTING RANGE OR TEMPERATURE [Internet]. Uspbpep.com. [cited 2023 Jun 13]. Available from: http://www.uspbpep.com/usp31/v31261/usp31nf26s1_c741.asp
[22] P. Bhatt, A. Kumar, and R. Shukla, "Nanorobots recent and future advances in cancer or dentistry therapy- A review," Am. J. PharmTech Res., vol. 9, no. 3, pp. 321–331, 2019.

[23] NOAA Office of Response, Restoration, Gov US. CHLORDIAZEPOXIDE HYDROCHLORIDE [Internet]. Noaa.gov. [cited 2023 Jun 13]. Available from: https://cameochemicals.noaa.gov/chemical/19973
[24] S. K. Sharma and P. Bhatt, "Controlled release of bi-layered EGCG tablets using 3D printing techniques," J. Pharm. Res. Int., pp. 5–13, 2021.

[25] Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions. Choice (Middletown) [Internet]. 2007;44(09):44-4794-44–4794. Available from: http://dx.doi.org/10.5860/choice.44-4794
[26] A. Kumar, P. Bhatt, and N. Mishra, "Irritable bowel Syndrome with reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review," J. Chem. Pharm. Sci., vol. 12, no. 03, pp. 71–78, 2019.

[27] Anderson W, Kozak D, Coleman VA, Jämting ÅK, Trau M. A comparative study of submicron particle sizing platforms: accuracy, precision and resolution analysis of polydisperse particle size distributions. J Colloid Interface Sci [Internet]. 2013; 405:322–30. Available from: http://dx.doi.org/10.1016/j.jcis.2013.02.030
[28] P. Bhatt et al., "Plasma modification techniques for natural polymer-based drug delivery systems," Pharmaceutics, vol. 15, no. 8, 2023.

[29] Shekunov BY, Chattopadhyay P, Tong HHY, Chow AHL. Particle size analysis in pharmaceutics: principles, methods and applications. Pharm Res [Internet]. 2007;24(2):203–27. Available from: http://dx.doi.org/10.1007/s11095-006-9146-7
[30] P. Bhatt et al., "Functional and tableting properties of alkali-isolated and phosphorylated barnyard millet (Echinochloa esculenta) starch," ACS Omega, vol. 8, no. 33, pp. 30294–30305, 2023.

[31] Newman AW, Reutzel-Edens SM, Zografi G. Characterization of the "hygroscopic" properties of active pharmaceutical ingredients. J Pharm Sci [Internet]. 2008;97(3):1047–59. Available from: http://dx.doi.org/10.1002/jps.21033
[32] C. Baskar, S. Ramakrishna, and A. Daniela La Rosa, Eds., Encyclopedia of green materials. Singapore: Springer Nature Singapore, 2022.

[33] Thepharmajournal.com. [cited 2023 Jun 13]. Available from: https://www.thepharmajournal.com/vol4Issue5/Issue_july_2015/4-4-9.1.pdf.