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Exploring effect Of Mesoporous Carrier in improving in-vitro performance of Dronedarone HCl Formulation

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KEYWORDS

Dronedarone Hydrochloride, MMT, Syloid, poor water solubility, Dissolution

ABSTRACT:

Introduction: Dronedarone HCl, a versatile antiarrhythmic drug for atrial fibrillation, has poor aqueous solubility and dissolution, resulting in less 0ral bi0availability of nearby 4% lacking meal, and rises to 15% with a high-fat meal.

Objectives: This study investigated the complexation of DRN HCl with Montmorillonite (MMT) & SYLOID® 244FP as a mesoporous carrier to increase the solubility and dissolution-rate.

Methods: Physical blends developed using mix them accurately weighed quantity of dronedarone hydrochloride with MMT & SYLOID®244FP in a glass mortar. These complexes were characterized by FTIR, DSC, and P-XRD, showing different properties from the pure drug. The physical mixture was evaluated for solubility study to optimize the ratio. Different type of medium intended for the s0lubility study (buffers of pH1.2, pH4.5, pH6.8 & water) at 37˚C.

Results: The solubility of batch B2 (Drug: MMT,1:2) increased twofold compared to batch B1 (Drug: MMT,1:1), while batch B4 (Drug: Syloid,1:2) showed a onefold increase over batch B3 (Drug: Syloid,1:1). Therefore, Batch B2 was selected for further formulation. The optimized drug: carrier (1:2) ratio was selected, with MMT being a better carrier than syloid. The formulation can be optimized by using 2^2 factorial design. The optimized mixture's tablet form significantly increases drug release in at pH4.5 and 6.8 compared to standard by using pure drug.

Conclusions: So, the overall results suggest that complex of drug-MMT may be potentially useful in the preparation of novel pharmaceutical formulation containing DRN HCl. Also, this mesoporous carrier can protect the drug at lower pH which is one of the reasons for its limited oral bioavailability.

1. Introduction

Cardiac arrhythmia, particularly atrial fibrillation, is prevalent among older adults and typically requires ongoing antiarrhythmic medication to maintain normal sinus rhythm due to its chronic nature and high recurrence rate [1]. Antiarrhythmic drugs such as amiodarone can cause side effects like thyroid, pulmonary, and liver toxicity, along with severe ventricular arrhythmia [2]. Treatment for atrial fibrillation, a frequent persistent arrythmia, primarily focuses on treating the underlying conditions, controlling rhythm, rate, and thromboembolic events to prevent strokes and manage symptoms.

For many conditions, oral treatment is the most effective method. However, the therapeutic effect of insoluble drugs is often reduced due to their low bioavailability [3]. Intestinal permeability and water solubility are crucial parameters governing oral bioavailability, absorption, and solubility of all compounds [4].

The pharmaceutical industry faces challenges with the water solubility of drugs like griseofulvin, indomethacin, carbamazepine, phenytoin, and digoxin [5]. Therefore, several investigations are carried out to speed up the rate at which poorly soluble medications dissolve, to boost their efficacy, and to concurrently lower their dosages, so mitigating their hazardous effects [6].

Common strategies to improve drug solubility include micronization, pH adjustment, solid dispersion, chemical modification, forming the complex with compounds like cyclodextrin and its derivative and micellar solubilization [7].

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To enhance the drug release of poorly soluble medication solid-dispersion technique is best way which was developed in the 1970s. This is dispersing poorly soluble drugs on hydrophilic carrier [8]. The primary techniques for preparing solid dispersions are hot extrusion, solvent evaporation and melting. Drug solubility enhancement is achieved through improved chemical wettability, conversion from crystalline to more soluble non-crystalline forms, increased surface area and reduced particle size [9].

Dronedarone HCl is a versatile and well-known antiarrhythmic drug for the treatment of atrial fibrillation, it has poor water solubility and dissolution rate. Due to its significant presystemic metabolism and poor water solubility, dronedarone HCl has a less 0ral bi0availability of around 4% lacking meal and rises nearly 15% when given with high-fat meal. At lower GI pH that is less than pH 3 this drug is reported to be degraded fast which is one of the reasons for its very less oral bioavailability. It is primarily used to help individuals with paroxysmal or chronic atrial fibrillation return to normal sinus rhythm [10]. Dronedarone HCl is a multichannel blocker that controls atrial fibrillation's rhythm and rate, just like amiodarone. It satisfies the requirements for all four Vaughan Williams antiarrhythmic medication classes because it inhibits β-adrenergic receptors and blocks potassium, calcium, and sodium ion channels.

Amiodarone and dronedarone these are related benzofuran compounds, dronedarone's chemical structure lacks the iodine groups that are associated with the thyroid problems caused by amiodarone. It is chemically N-(2-Butyl-3{4-[3(dibutylamino)propoxy] benzoyl}-1-benzofuran-5-yl)methanesulfonamide hydrochloride and molecular weight is 556.758 g/mol.Dronedarone HCl is a white crystalline powder that dissolves in acetonitrile and methanol but does not dissolve in water. The melting point is 140-145 °C

As per BCS, dronedarone HCl categorized as class-II drug because of its high permeability and limited water solubility. The goal of the current study was to create a complex containing mesoporous carriers such as SYLOID® 244 FP and Montmorillonite (MMT) in order to assess enhanced dronedarone HCl solubility and dissolving rate. Also, protect the drug at a lower pH.

Mesoporous Silica nanoparticles (MSiNPs):
Amorphous substances with a spherical form can be created in various shapes and sizes, with surface properties that are easily modified for different purposes. Mesoporous silica is distinguished by its mesoporous structure, which has pores with diameter ranging from 2 ro 50 nm. Microporosity is between the ranges of microporous and microporous materials, according to IUPAC. It is possible to create these mesoporous particles by spray-drying or simple sol gel technique.
Extensive data on physicochemical properties, safety, toxicology, ecotoxicology, and epidemiology indicate no environmental or health risks associated with these materials. They are considered non-toxic and generally recognized as safe for use in medicines. MSNs are a auspicious drug delivery vehicles of their exceptional structure. They offer a high surface area, large pore volume, chemical and systemic stability, excellent biocompatibility, high hydrophobicity, resistance to pH changes, multifunctionality, non-toxicity, and biodegradability.

In this study, we chosen MMT and SYLOID® 244FP as carriers. Montmorillonite, often known as clay, is a soft phyllosilicate mineral group that precipitates out of aqueous solutions as microscopic crystals. Known by its French name, Montmorillonite, is a 2:1 clay belonging to the smectite group. It is made up of two tetrahedral silica sheets encircling an octahedral alumina sheet. The clay particles have a plate-like form and have an average thickness of 0.96 nm and diameter of around 1 μm. Identifying individual clay particles requires an electron microscope with approximately 25,000 times magnification. This category includes minerals like saponite, nontronite, beidellite, and hectorite.

SYLOID® 244FP (S244) silica is an effective carrier due to its unique particle structure and morphology. It features a highly developed pore network, offering an ultra-high surface area and adjustable pore sizes ranging from 2.5 to 3.7 μm. These characteristics contribute to its high drug-loading capacity and make it an excellent agent for enhancing dissolution [11-16]

The present study is focused towards the substantial improvement of dissolution of DRN HCl with optimal and promising release pattern when administered orally.

2. Materials & Methods

Materials:

Apparatus: UV-Vis Spectrophotometer (SHIMADZU-1800) FTIR (Jasco M-4100), Weighing balance (AUX220), Bath sonicator (BIOMEDICA BMI-599F), PH-meter (Auto Digital pH- meter), Dissolution test apparatus (Electrolab TDT-06L) was used for research study. Glassware like pipettes, beakers, and volumetric flasks were used.

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Chemical and reagent: Dronedarone hydrochloride was received from Emcure Pharmaceuticals Pune. Montmorillonite (MMT) & SYLOID® 244FP was purchased from Sigma Aldrich. Sodium starch glycolate was kindly supplied by Alembic Pharmaceuticals Ltd. Talc & Mg stearate were received from Emcure House MIDC, Pune. All other chemicals and reagents utilized were of analytical grade.

Methods:

Physical mixture preparation: A physical mixture of dronedarone hydrochloride with MMT & SYLOID® 244FP was prepared by the physical mixing technique. Physical mixtures (PM) were prepared by carefully combining precisely weighed volumes of dronedarone HCl with MMT & SYLOID® 244FP after crushing in a glass morter as shown in Table 1. Then this mixture was in an orbital shaker for 24 hrs.

Table 1. Preliminary batches for optimum drug-to-carrier ratio

Batches	B1	B2	B3	B4
Drug	DRN HCl	DRN HCl	DRN HCl	DRN HCl
Carrier	MMT	MMT	SYLOID	SYLOID
Amount of drug (gm)	0.5	0.5	0.5	0.5
Amount of carrier (gm)	0.5	1	0.5	1
Drug carrier ratio	1:1	1:2	1:1	1:2

Preformulation study

The following pre-formulation studies were performed.
Identification of drug

Organoleptic properties:
The drug was observed for its color, odor, structure,& physical description.

Determination of melting point: The melting point of the drug was measured by sealing one end of a capillary tube caontaining a small amount of the sample. A melting point equipment with a capillary tube was used to measure the temperature at which the target medication melted. The average value was recorded after this was done three times.

Determination of solubility of pure drug and physical mixture:

Studies were performed to optimize the ratio between the drug and the carrier. A physical mixture of the drug with each carrier was prepared and analyzed three times. The solubility of DRN HCl was tested in a USP buffer containing different solutions such as pH 6.8, pH 4.5, pH1.2 buffers, and water at 37^0C. The process involved weighing 10 mg of DRN HCl into each vial, adding 10 mL of USP buffer, equilibrating at 37˚C, filtering, and analyzing the concentration using a UV spectrophotometer. The results of the ratio optimization study provided the basis for selecting the optimized DRN HCl carrier ratio. Results are shown in table no.4

Identification of DRN HCl:
10 mg DRN HCl was dissolved in 100 ml water and further diluted to get 50ug/ml concentration of the drug and examined in the range 200 nm to 400 nm. It shows an absorption maximum of 290nm. Figure no.1 A shows lamda max at 290 nm.

Preparation of calibration curve of DRN HCl:
To make a stock solution, 10 mg of DRN-HCl was dissolved in a 100 ml volumetric flask with 75 mL of acetate buffer at pH 4.5 and 25 mL of methanol, creating a concentration of 100 mcg/ml. Aliquots of 1,1.5,2.2.5 and 3 ml from this stock solution were then transferred into a separate 10 ml volumetric flask and diluted to the mark with phosphate buffer at pH 4.5. When scanned in the UV range (200nm to 800nm), the maximum absorbance of DRN HCl in pH4.5 buffer was found to be 290nm, using a blank sample for comparison in a UV-visible spectrophotometer. The absorbance of this solution was measured at 290 nm, and a graph of concentration versus absorbance was plotted. The absorbance of this solution was measured at 290 nm, and a graph of concentration vs absorbance was plotted The same method was used for buffers of pH 1.2 & 6.8 to create a calibration curve. Calibration plots are shown in Figures 1B,2A, and 2B.

Compatibility study:

FTIR:

The interaction between the drug and excipient was studied by FTIR. This study was used to evaluate the drug's compatibility. After the pure medication mixture had been well combined, it was placed under Bruker FTIR scanning in the 400–4000 cm–1 wavelength range. The spectra were examined and deciphered. Figures 3A & B show FTIR graphs for pure drug and physical mixture.

DSC (Differential Scanning Calorimeter):

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A DSC was used to obtain a DSC thermogram of physical mixes and DRN HCl. 20-25 mg samples were loaded onto aluminum pans & put into the DSC chamber. The samples were subjected to a temperature range from 30^0C to 300^0C, with a heating rate of 10^0C per minute. The DSC overlay is illustrated in Figure 4.

Powder X-ray Diffraction (PXRD):

PXRD patterns for both empty and drug-loaded MMT were obtained using a Rigaku Ultima IV diffractometer at SPPU, Pune. The measurements were conducted within a 2θ range of 5˚ to 80˚, with a scan speed of 10˚ per minute. Figure no. 5 shows the PXRD graph.

Formulation of directly compressible tablet formulation:

As indicated in (table 2), tablets were made utilizing the direct compression method with 2^2 factorial designs. Each ingredient (as shown in the table no.2) was ground into a powder and put through sieve number 16 on its own. A tiny amount of the medication and the immediately compressible excipient were added at a time, blended, and set aside to create a homogenous combination. The remaining ingredients were then mixed in a geometrical pattern. Magnesium stearate and talk were the final ingredients added and mixed for 2 minutes.The tablets,each weighing 400mg , were then compered using flat round punches ranging from 8 to 12 nm in diameter.

Optimization of tablet formulation by using 2^2factorial design:

Table 2. Composition of tablet

Ingredients	F1	F2	F3	F4
Drug: carrier	1:2	1:2	1:1	1:1
PEG 6000	50	50	50	50
SSG	9	4.5	9	4.5
MCC	32	36.5	132	136.5
Mg. Stearate	3	3	3	3
Talc	6	6	6	6
Total in mg	**400**	**400**	**400**	**400**

In this method, we prepared 4 different batches to optimize the formulation.2^2Full factorial method is employed to assess the impact of independent variables on dependent variable. Independent variables like drug with carrier ratio & concentration of SSG and Dependent variables like % Drug release, Disintegration time & Hardness. Table no. 5 shows optimization results.

Evaluation of optimized formulation against the standard formulation (Using pure drug)

Table 3. Evaluation of optimized formulation against the standard formulation Using pure drug

Sample	Batch-1 (With carrier)	Batch-2 (pure drug)
Physical mixture (1:2) (Drug:MMT)	300mg	-
PEG 6000	50mg	-
Pure drug	-	100 mg
Lactose	-	250 mg
Microcrystalline cellulose (MCC)	32 mg	32 mg
Sodium starch glycolate (SSG)	9 mg	9 mg
Mg. stearate	3 mg	3 mg
Talc	6 mg	6 mg
Total	**400 mg**	**400 mg**

Evaluation of the optimized tablet

Precompression parameters:

The pre-compression characteristics of the pure drug and powder blend, such as angle of repose, bulk and tapped densities, compressibility index, and Hausner ratio, were assessed prior to compression. The angle of repose was measured using the funnel method, where the powder was weighed and allowed to flow freely onto a surface. Bulk and tapped densities were measured by placing 2 grams of powder into a 10ml measuring cylinder and tapping it onto a hard surface. Hausner's ratio, an indicator of the flowability of powder or granular material, was calculated as the ratio of tapped density to bulk density. These parameters were evaluated both before and after the addition of lubricants to compare the inherent flow properties of the powders.

Weight variation test:

A random sample of twenty tablets from various formulations was taken, and their average weight was determined using a digital balance. The results were expressed as mean±SD. As per USP guidelines, the tablets are considered acceptable if no more than two tablets surpass the allowed percentage limit and no single tablet deviates by more than twice the specified range.[17]

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Measurement of Thickness:

For each formulation, ten tablets were selected and their thickness was measured with a screw gauge. The average Thickness and standard deviation(mean±SD) were recorded. The thickness variation should not exceed ±5% of the specified standard value.[18]

Measurement of Hardness:

The hardness of tablets from various formulations was evaluated using a Monsanto hardness tester. In this device, a spring is compressed between two plungers. The lower plunger touches the tablet, and the upper plunger applies force until the tablet fractures. [19, 20, 21]

Friability:

The friability test was carried out using a Roche friabilator, a device designed for evaluating tablet durability. Ten tablets were weighed and placed into the fribilator's chamber, which rotates at 25 rpm. During rotation, the tablets are dropped from a height of 6 inches with each revolution. The test continued for 100 revolutions over a span of 4 minutes. After testing, the tablets were cleaned and reweighed. The percentage of weight loss was then calculated, with the acceptable friability limit set at a maximum of 1%. [22, 23]

The formula used to calculate friability is:

Friability (%) $=(W_1-W_2)*100/W_1$

Here; W_1 and W_2 indicate the initial and final weight of the tablet

Disintegration time

The disintegration time test involves placing six tablets in a basket-rack assembly, each with a disk, and immersing them in a liquid medium. The apparatus moves the basket at a rate of 28 to 32 cycles per minute and records the time required for each tablet to disintegrate completely. If any tablets fail, an additional six tablets are tested; if they also fail, the batch does not meet the disintegration test requirements.

In-vitro drug release study:

Dissolution testing of pure DRN HCL and its physical mixture with the carrier was carried out in triplicate using USP Apparatus 2. The testing was conducted at 75 rpm with 900 ml dissolution medium, which included acetate buffer(pH 4.5)and phosphate buffer9pH 6.8) at a temperature of 37± 0.5^0 C. A sample equivalent to 100mg of the drug was used for the study. The dissolution process lasted for 90 minutes, with 5 ml samples taken at Intervals of 15,30,45,60,75, and 90 minutes. Each withdrawn sample was replaced with the same volume of fresh medium to maintain a constant volume. Drug dissolution was measured using spectroscopy [24]

Accelerated stability study:

In accordance with ICH-Q1A guidelines, the stability of the optimized formulation was evaluated by storing it at 40^0C ± 2^0C and 75% RH 5% for a duration of 3 months. The stability studies involved examining the prepared tablet for changes in physical appearance, hardness, and drug release properties. [25, 26, 27]

3. Result

Preformulation study of the drug:

The pure DRN HCl drug is a solid white powder with an odorless characteristic. It exhibits solubility in methanol and acetonitrile but is insoluble in water. Its melting point ranges between 140 to 145 °C. Overall, it is a non-volatile, white powder that dissolves in certain organic solvents but not in water, and it melts within a defined temperature range.

Solubility of pure drug:

The results of pure drug indicate that the drug's solubility is highly dependent on the pH of the solvent, with the highest solubility observed in a mildly acidic environment (acetate buffer pH 4.5).

Evaluation of drug carrier complex:

The drug's solubility is highest in acetate buffer pH 4.5, suggesting a mildly acidic environment is most favorable for dissolving it. Its solubility is moderate at pH=6.8, & low in water and HCl.The variation in solubility across pH environments highlights the importance of solvent selection for optimal drug dissolution, potentially impacting bioavailability and therapeutic effectiveness. According to the solubility, the solubility of batch B2 (Drug: MMT,1:2) increased twofold compared to batch B1 (Drug: MMT,1:1), while batch B4 (Drug: Syloid,1:2) showed a onefold increase over batch B3 (Drug: Syloid,1:1). Therefore, Batch B2 was selected for further formulation. These results demonstrate that MMT is a more effective carrier for solubility enhancement compared to Syloid, making it a suitable choice for this purpose.

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Table 4. Solubility study of drug-to-carrier ratio

Solvent used	Pure drug mg/ml.	B1(mg/ml)	B2(mg/ml)	B3(mg/ml)	B4(mg/ml)
Water	≤0.1	0.364± 0.040	0.529± 0.025	0.325± 0.029	0.442± 0.037
Acetate buffer (pH=4.5)	≤0.5	3.39±0. 210	5.42±0. 238	3.57±0. 382	4.67±0. 374
Phosphate buffer(pH=6.8)	≤0.3	1.83±0. 179	3.92±0. 139	1.90±0. 284	2.98±0. 251
Hydrochloric acid(pH=1.2)	≤0.1	0.891± 0.035	1.47±0. 179	0.901± 0.030	1.13±0. 215

UV spectroscopy

Identification of DRN HCl

The UV spectrum of Dronedarone Hydrochloride shows prominent absorbance maxima at wavelength 290 nm (fig 1) which is similar to the standard peaks and therefore confirms the identity of sample drugs as Dronedarone HCl. The reported absorbance maxima of Dronedarone HCl was at 290 nm.

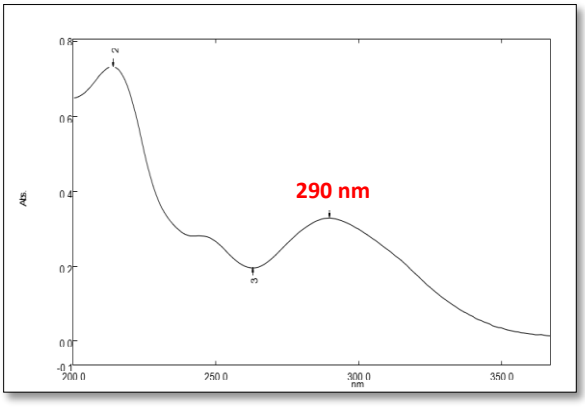

Figure 1. UV spectra of DRN HCl (290nm)

Calibration curve of DRN HCl in pH=4.5, pH=1.2 & pH=6.8

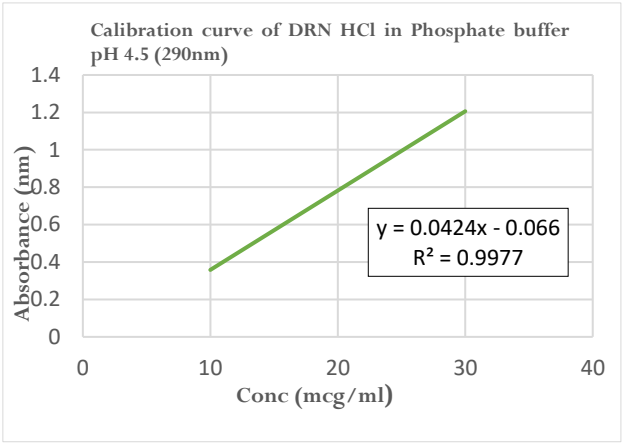

Figure 2. Calibration curve of DRN Hydrochloride in phosphate buffer pH=4.5

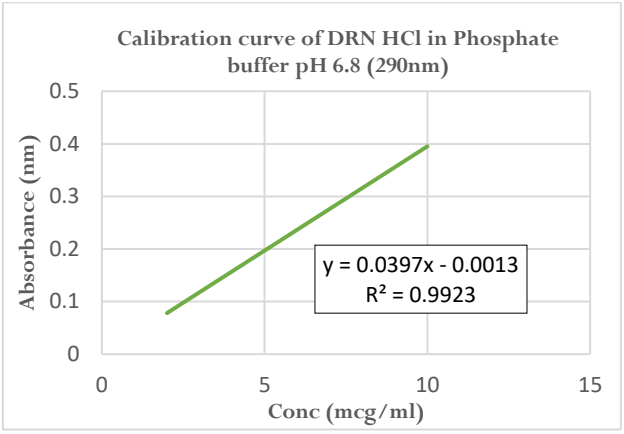

Figure 3. Calibration curve of DRN HCl in pH=6.8

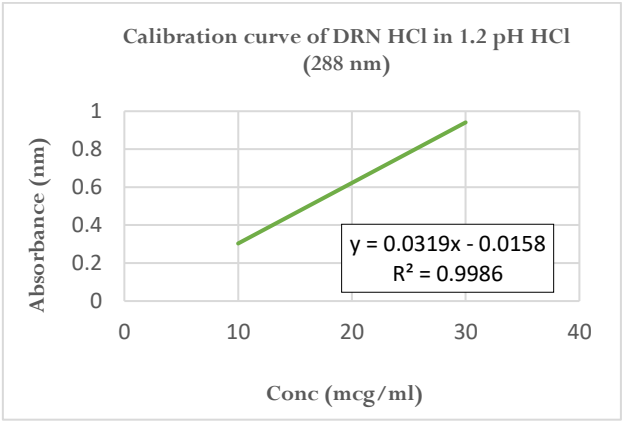

Figure 4. Calibration curve of DRN HCl in pH=1.2

FTIR Interpretation:

The presence of a doublet at 3406.29 cm^{-1} owing to the -

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NH stretch and peaks at 2932.83 and 2900.93 cm^{-1} owing to the -CH an -CH2 stretching vibration confirms the identification of the amide functional group. The symmetrical vibration peak of the S=O bond is the cause of the significant absorption peak at 1338.65 $cm^{-1.}$ The existence of an aromatic ring is indicated by peaks in the 900-600 cm^{-1} range. The inclusion complexes of the medication with MMT show a large peak in the IR spectra that overlaps the doublet peak for -NH2 at (3342.17 cm^{-1}). A possible cause of the signal at 2900.49 cm^{-1} is the CH bond. Peaks for the amide functional group's carbonyl C=O stretching are located at 1031.09 cm^{-1} and 1156.60 cm^{-1}. The C-Cl bond could be the cause of the peak at 781.27 cm^{-1}. An interaction between dronedarone HCl and MMT was shown by the shifting of a peak at 1075.32 cm^{-1}, which is a characteristic peak for drug S=O, to a higher frequency of 1338.65 cm^{-1}.

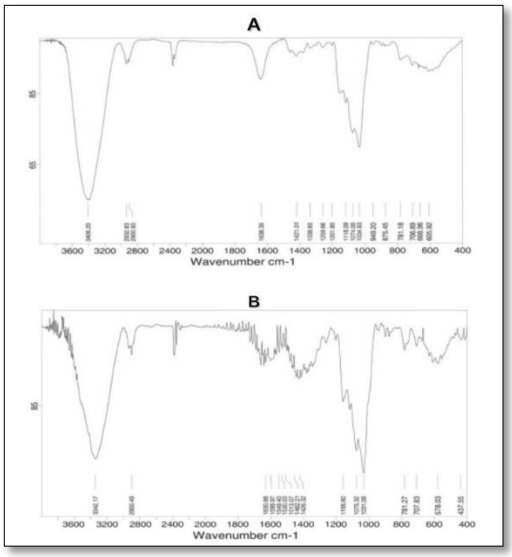

Figure 5. A-FTIR Analysis of pure DRN HCl & B- FTIR Analysis of pure DRN HCl and MMT

Differential Scanning Calorimetry (DSC):

The DSC curve offers insights into the thermal behaviour about the thermal behaviour of the pure drug and its corresponding drug-carrier system is illustrated in the figure.

X-Axis (Temperature, in Celsius): The horizontal axis represents the temperature range over which the sample was tested, from about 50°C to 350°C.Y-Axis (DSC signal, in mW/mg): The vertical axis represents the heat flow associated with the sample's transitions. This is typically measured in milliwatts per milligram (mW/mg).

The provided DSC overlay thermogram includes multiple curves representing different samples, allowing for comparison of their thermal behaviors. The samples include pure DRN HCl, MMT, physical mixture and tablet formulation. Here's an interpretation of the key features:
Pure DRN HCl (Green Curve): Endothermic peak at 45.1°C likely indicating a phase transition or melting. Another endothermic peak at 145.2°C (-16.08 mW) potentially related to decomposition or another phase transition.
MMT (Red Curve): The red curve shows minimal thermal events, indicating stability over the measured temperature range.
Physical Mixture (Purple Curve): Endothermic peak at 112.6°C potentially indicating an interaction between DRN HCl and MMT. And Endothermic peak, 137.7°C possibly corresponding to the melting point of DRN HCl.
Tablet Formulation (Blue Curve): Endothermic peak at 58.4°C might be related to a phase transition or melting of excipients used in tablet formulation. Endothermic peak at 142.6°C possibly indicating a similar event to the physical mixture, showing interaction within the formulation.

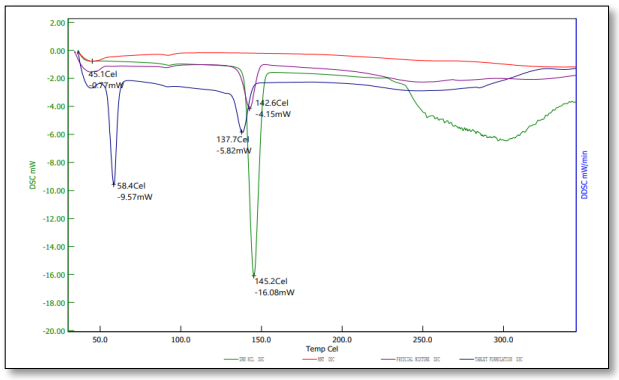

Figure 6. DSC overlay —DRN HCl —MMT — physical mixture — Tablet formulation

Powder X-ray Diffraction (PXRD):
The decrease in peak intensity indicated a modest reduction in the crystallinity of MMT following drug adsorption, which was evident at higher at higher drug concentration. Figure 7. demonstrates the MMT with lower peak intensities.

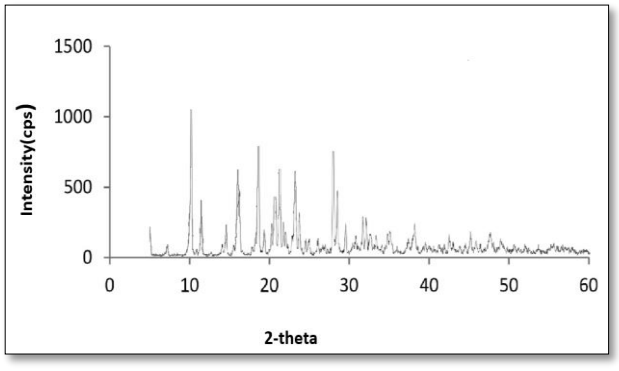

Figure 7. PXRD graph of drug and MMT complex

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Optimization by using 2^2factorial design:

To determine the optimized batch, we should consider the desired characteristics for each parameter: % drug release, disintegration time, and hardness. Generally, higher drug release, shorter disintegration time, and appropriate hardness (not too hard, not too soft) are preferred**.**

F1 has the highest % drug release and the shortest disintegration time, with an appropriate hardness. F2 has a decent % drug release but a longer disintegration time and higher hardness. F3 and F4 have lower % drug releases and longer disintegration times.

From these comparisons, Batch F1 is the optimized batch because it has the highest drug release (97%), a relatively short disintegration time (9 min), and a reasonable hardness (6 kg/cm²).

Table 5. Optimization by using 2^2factorial design

Batches	drug : carrier	Conc of SSG	% Drug release (90 min)	Disintegration time (min)	Hardness (kg/cm 2)
F1	1:2	9	97.83±0.35	9±0.5	6±0.20
F2	1:2	4.5	79±0.30	12±0.5	7±0.20
F3	1:1	9	72±0.30	10±0.5	6±0.20
F4	1:1	4.5	70±0.30	14±0.5	7±0.20

Assessment of the optimized tablets:

Pre-compression parameters:

The physical assessment pure DRN HCl reveals excellent flow properties,enablingits use in direct compression. The drug powder and tablet blend show good flow properties, with the drug powder showing a slightly better angle of repose. The drug powder has a higher bulk density, indicating a denser packing of particles. The drug powder has a slightly better compressibility index, while the tablet blend has a lower value. The drug powder also has a good Hausner's ratio, with a slightly better ratio. Both samples meet the required specifications. Results are displayed in Table 6.

Table 6. Pre compression parameter

Sr. no.	Parameters	Drug powder	Tablet blend	Comment
01	Angle of repose	25º18’	30˚19’	Good
02	Bulk Density	0.476±0.05 gm/cm3	0.410 ± 0.02 gm/cm3	Comply
03	Tapped Density	0.557±0.02 gm/cm3	0.483 ± 0.05gm/cm3	Comply
04	Compressibility index	14.54± 0.84	15.113 ± 0.75	Good
05	Hausner’s Ratio	1.1430 ± 0.03	1.1780± 0.02	Good

Post-compression parameters:

The table evaluates tablets' physical and mechanical properties, ensuring they meet the required standards. The average hardness is 6 ± 0.080 kg/cm², indicating strength without brittleness. The thickness is 1.22 ± 0.02 mm, ensuring uniformity in size. The diameter is 3.32 ± 0.02 mm, meeting the specified standards. Friability is 0.50%, indicating durability without significant degradation. The disintegration time is 9 minutes, ensuring proper drug release and absorption. The weight variation test confirms uniformity, ensuring consistent dosage. Results are displayed in table-7

Table-7 post-compression parameters

Sr. No	Evaluation parameter	Average	Comment
1	Hardness (kg/cm²)	6 ± 0.080 kg/cm²	comply
2	Thickness (mm)	1.22 ± 0.02mm	comply
3	Diameter (mm)	3.32 ± 0.02 mm	comply
4	Friability (%)	0.50±0.01%	comply
5	Disintegration time (min)	9±0.5 min	comply
6	Weight variation test	3.3± 0.1%	comply

In- vitro drug release study:

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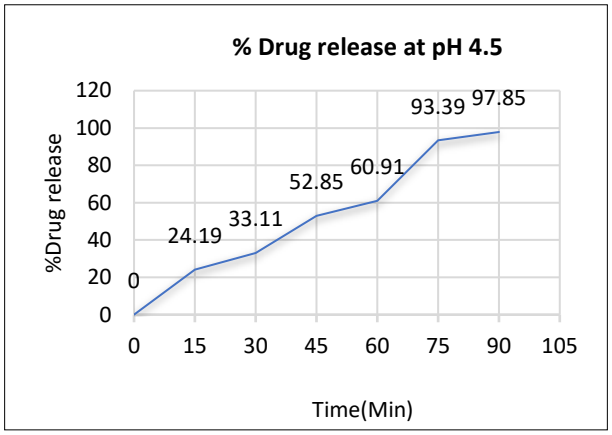

Figure 8. Drug release of optimized formulation at pH=4.5

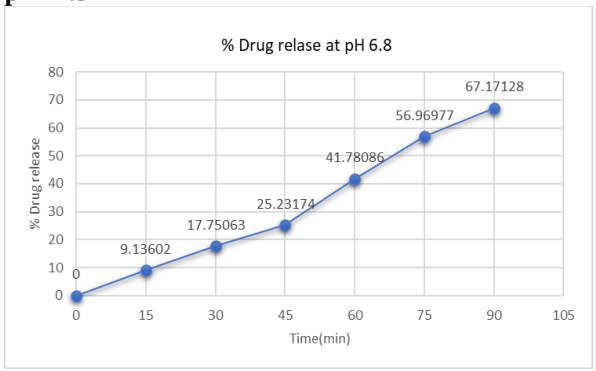

Figure 9. Drug release of optimized formulation at pH=6.8

Comparison of optimized formulation with standard formulation (using pure drug)

Table.8. In-vitro drug release

Drug release in acetate buffer(pH=4.5)			**Drug release in Phosphate buffer(pH=6.8)**		
Time (min)	% Drug Release (with carrier)	% Drug Release (Pure drug)	Time (min)	% Drug Release (with carrier)	%drug release (Pure drug)
15	24.19 ± 0.20	5.57± 0.15	15	9.13±0.10	4.23±0.10
30	33.11 ± 0.10	11.92± 0.15	30	17.75±0.15	12.2±0.20
45	52.85 ± 0.15	26.43± 0.25	45	25.23±0.15	25.8±0.20
60	60.91 ± 0.10	30.2±0.20	60	41.78±0.20	31.3±0.20
75	93.39 ± 0.20	37.31±0.20	75	56.96±0.15	35.2±0.20
90	97.85 ± 0.20	43.2±0.20	90	67.17±0.15	41.3±0.20

Invitro drug release studies were conducted in an acetate buffer(pH=4.5). The findings revealed a significant difference between the release profiles of tablets containing pure Dronedarone HCl and those with physical mixtures (PMs) incorporating various carriers. Tablets with pure DRN HCl showed dissolution of 43.2±0.20 % in 90 minutes. And approximately pure drug require three hours for complete release. Dronedarone HCl released from tablets prepared with complex of druh with MMT showed dissolution of 97.85±0.20 % in 90 minutes. The drug release were also undertaken at pH 6.8(Table no. 8). In basic pH tablets with pure DRN HCl showed dissolution of 41.3±0.20 % in 90 minutes. Dronedarone HCl released from tablets prepared with MMT loaded particles showed dissolution of 67.17±0.15% in 90 minutes.

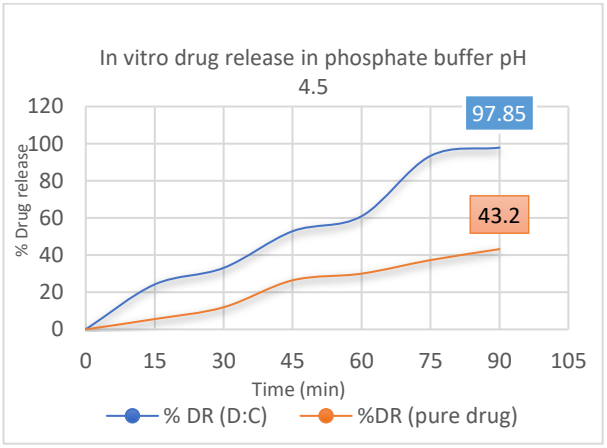

Figure 10. Comparison of the optimized formulation with the standard formulation at pH 4.5

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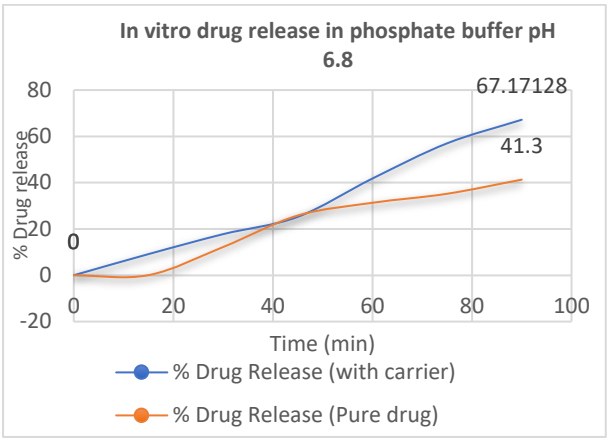

Figure 11. Comparison of the optimized formulation with the standard formulation at pH 6.8

Accelerated stability study:

A 90-day stability study of a drug formulation over 90 days showed that the tablets remain relatively stable, with minor changes in drug release and disintegration time.The study suggests these minor changes may indicate minor formulation changes or interactions, but are likely within acceptable limits for many pharmaceutical products.

Conclusion

In the present work, the MMT and Syloid were attempted in the compressed tablet to enhance solubility and stability of DRN HCl at lower pH in the GI tract when administered orally. This study includes to increase the dissolution of DRN HCl in the GI tract, a novel physical mixture system was prepared by molecularly dispersing the active compound into MMT and syloid. The optimized mixture system consisted of the drug and carrier in as 1:2 ratio. According to the evaluation of the drug carrier complex it was observed that MMT has shown more promising results over syloid. Therefore, MMT is further evaluated for formation of compressed tablet of DRN HCl. The prepared formulation was optimized by using 2^2 factorial design. According to the optimization result, batch F1 is the optimized batch because it has the highest drug release, a relatively short disintegration time, and a reasonable hardness.

The tablet form of the optimized mixture significantly increases drug release at pH 4.5 and 6.8 as compared to standard by using pure drug.

So the overall results suggest that the complex of drug with MMT may be potentially useful in the preparation of novel pharmaceutical formulations containing DRN HCl. Also, this mesoporous carrier can protect the drug at low pH which is one of the reason for its limited oral bioavailability.

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Ethics statement: None.

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