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Development and Evaluation of Immediate Release Pellets Using Solid Dispersion Technique for Solubility Enhancement of Poorly Soluble Drug

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Abstract:

The present study was aimed at the formulation and evaluation of immediate-release pellets of Meclizine HCl, a poorly water-soluble drug, using the extrusion–spheronization technique. The objective was to enhance solubility, improve dissolution rate, and achieve rapid disintegration. SoluPlus® and D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) were used as solubilizing and absorption-enhancing polymers, along with excipients such as microcrystalline cellulose, dicalcium phosphate, sodium starch glycolate, and lactose monohydrate. the prepared pellets were evaluated for micromeritic properties, friability, and disintegration time, and further characterized by ATR, DSC, XRD, and SEM studies. The results showed that the pellets exhibited good flow properties, mechanical strength, and uniform spherical shape. ATR analysis confirmed the absence of drug–excipient interaction. SEM images revealed smooth and spherical morphology of the pellets. Solid-state characterization indicated a reduction in drug crystallinity, contributing to enhanced solubility. in-vitro dissolution studies demonstrated that formulations containing both SoluPlus® and TPGS exhibited significantly improved drug release and faster disintegration compared to conventional formulations. The combined effect of these polymers enhanced the overall performance of the formulation. Hence, the study concludes that the use of SoluPlus® and TPGS is an effective approach for improving solubility, dissolution, and immediate-release characteristics of Meclizine HCl pellets.

Kye words: SoluPlus®, Pellets, Meclizine, Solubility enhancement,

I. Introduction

The oral route is the most common way to give drugs due to patient compliance,cost and simplicity of administration. However, the therapeutic efficiency of many oral drugs is sometimes limited by their poor water solubility, which results in a low dissolution rate and low bioavailability. Class II of the Biopharmaceutics Classification System (BCS), which characterizes medications with high permeability but low solubility, includes many recently produced therapeutic compounds. Since the dissolving rate becomes the rate-limiting stage in medication absorption, improving solubility is an essential part of developing pharmaceutical formulations for such pharmaceuticals (Vasconcelos et al., 2007)

Many formulation techniques have been made to make medications that not dissolve well more soluble and faster to dissolve. These include solid dispersion, salt production, complexation, and particle size reduction. Solid dispersion is one method that has gotten a lot of attention as a useful and popular way to make hydrophobic drugs more soluble. In solid dispersion systems, the drug is spread out in a hydrophilic carrier matrix that makes it easier to wet, lowers the amount of crystals, and increases the surface area. All of these things speed up the drug's rate of dissolution. (Chiou & Riegelman, 1971).

Hydrophilic polymers are needed for solid dispersions because they make the drug particles easier to wet and disperse. In recent years, a number of advanced polymeric carriers have been made just for uses that involve making things more soluble. One of these polymers is Soluplus®, an amphiphilic graft copolymer made up of parts of polyethylene glycol, polyvinyl acetate, and polyvinyl caprolactam. Soluplus® is often used in drug formulations because it can make micelles in water and help drugs that not dissolve well in water dissolve better. This polymer can interact with both

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hydrophilic and hydrophobic molecules because it is amphiphilic. This makes solid dispersions more stable and helps them dissolve better. (Linn et al., 2012).

Another important excipient used in solubility enhancement is D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS). TPGS is a water-soluble derivative of natural vitamin E that is mostly used as an , solubilizer, emulsifier and absorption enhancer in pharmaceutical formulations. It can improved drug solubility by forming micellar structures and enhancing the wetting properties of hydrophobic drugs. furthermore , TPGS can inhibit P-glycoprotein efflux pumps, which enhance the gastrointestinal system's ability to absorb drugs. Because of these multifacted qualities, TPGS has attracted a attention in the development of poorly soluble drugs (Zhang et al., 2010).

One of the BSC class II drug which having poor solubility is meclizine hydrochloride, a well-known antihistaminic in the piperazine class. It is commonly used to treat vestibular disease-related nausea, and vomitingmotion sickness, vertigo. Despite its therapeutic efficacy, meclizine HCl has limited water solubility, which may limited rate of dissolution and consequently affect its bioavailability. Therefore, enhancement of solubility and rate dissolution of meclizine HCl is essential to enhancing its therapeutic efficacy. Using solid dispersion systems with suitable polymeric carriers is one crusial method to overcome this limitation.

The pharmaceutical industry has recently shown a great deal of interest in pelletization technology. Pellets are spherical particles,free-flowing that typically range in size from 500 to 1500 µm. Multiparticulate pellet systems having several advantages over conventional single-unit dosage forms, such as uniform drug distribution, reduced risk of dose dumping, improved flow characteristics, increased content homogeneity, and variable dosage form design. Furthermore, pellet systems' large surface area can enhance the characteristics of drug release and disintegration (Ghebre- Sellassie, 1989).

Immediate release pellet formulations are especially helpful for drugs that need to start working quickly . When solid dispersion techniques are used to incorporated the poorly soluble medications into pellet systems, the drug dissolution rate can be greatly sped up by the combination of a larger surface area and a higher solubility. Pelletized dosage forms are also flexible and good for making large amounts of medicine because they can easily be filled into capsules or compressed into tablets.

Consequently, the current study focus on the formulation and assessment of immediate-release pellets aimed at inhances the solubility of poorly soluble drugs. This study made solid dispersions of meclizine HCl using hydrophilic polymeric carriers like Soluplus® and TPGS to make the drug more soluble and dissolve immediate . The solid dispersions that were made were used to make pellets that release their contents faster . In vitro dissolving tests and a range of physicochemical characteristics were used to see how well the new formulations improved the solubility and release profile of meclizine HCl.

II. Material And Method

2.1Materials

Meclizine HCL munificently gifted by Srikem laboratory Pvt. Ltd. ,SoluPlus® BASF Pharma, Mumbai, India. TPGS was bought from Sigma-Aldrich, India, MCC pH 101 & Cross carmalose sodium Research Labs, Mumbai, India. Methanol was obtained from Merck Specialities Pvt. Ltd. Worli, Mumbai, India

Method

2.3Preparation of solid dispersions by Solvent evaporation method

A solid dispersion of Meclizine hydrochloride was prepared using SoluPlus® and TPGS (D-alpha tocopheryl polyethylene glycol 1000 succinate) by the solvent evaporation method. In this process, 400 mg of Meclizine hydrochloride (drug) and 400 mg ofSoluPlus® (polymer) and 200 mg of TPGS were taken in a porcelain dish , and methanol was added as a solvent to dissolve all components. The mixture was heated on a water bath at 80°C until a clear solution was formed. After obtaining the clear solution, it was allowed to cool at room temperature, leading to the formation of a solid mass as the solvent evaporated. The solid mass was then dried in a hot air oven until it completely dried and converted into a fine powder. This final dried powder represented the prepared solid dispersion.

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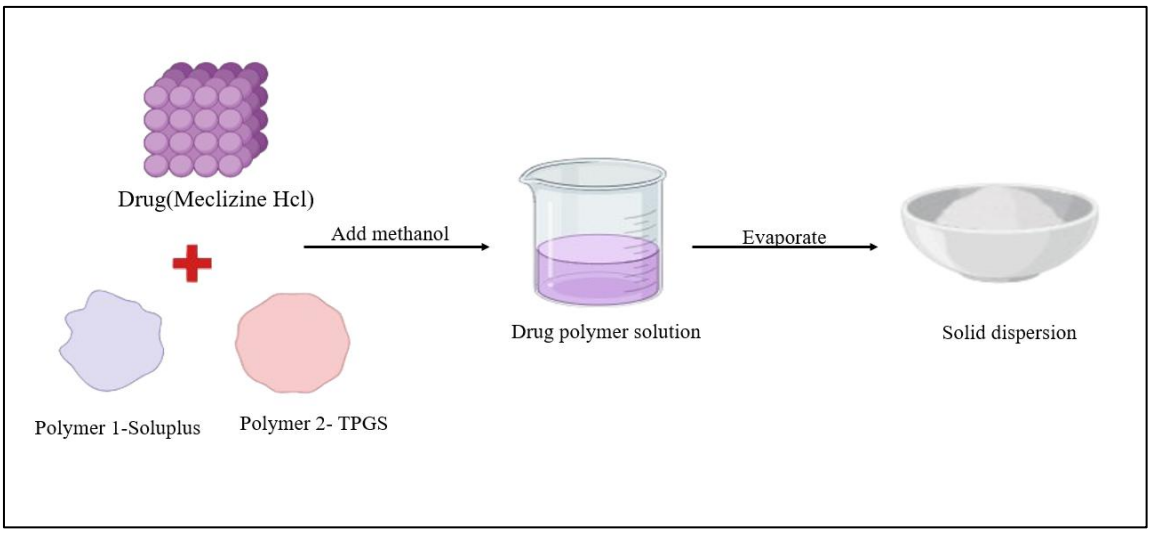

Figure 1: Preparation of solid dispersions

2.3Preparation of pellets by extrusion spheronization

Meclizine HCl pellets were prepared using a solid dispersion approach with Soluplus® and TPGS to improve the solubility. The solid dispersion was prepared by an appropriate method (solvent evaporation), and the optimized dispersion was used for pellet formulation. For pellet preparation, the required quantity of solid dispersion equivalent to the drug dose was accurately weighed and mixed with microcrystalline cellulose (Pharmacel-112) as a pelletizing aid and crosscarmellose sodium as a superdisintegrant. The dry powders were mix uniformly for about 10 minutes to ensure homogeneity. A suitable quantity of granulating liquid (purified water) was gradually added to the powder mixture with continuous mixing to obtain a uniform wet mass (dough). The prepared wet mass was then processed using an extrusion–spheronization technique. The wet dough mass was pass through a screw extruder fitted with a suitable mesh (approximately 1.5-2 mm) at 75 rpm for 20 minutes to produce cylindrical extrudates. The extrudates were immediately transferred to a spheronizer equipped with a crosshatch plate and spheronized(Innovative UICE, Umang Pharmatech Pvt Ltd, Mumbai, India) at optimized speeds (e.g., 800–1200 rpm) for a specific time of duration (10–20 minutes) to obtain spherical pellets. The prepared pellets were then dried in a hot air oven at 40–50°C for 2 hr. until a constant weight was achieved.The pellet formulation batches were prepared 3^2 full factorial design (Design-Expert® software Version 13.0.0) to evaluate the influence of two selected factors (independent variables): the quantity of Microcrystalline Cellulose (Pharmacel-112) (X_1) and Cross-carmellose sodium (X_2), pellets were made at three different levels (low, medium, and high). Three responses (dependent variables), drug release (Y1), pellet size (Y2), and disintegration time (Y3), were considered for each sample. The formulations designed by design expert software are F1–F9.

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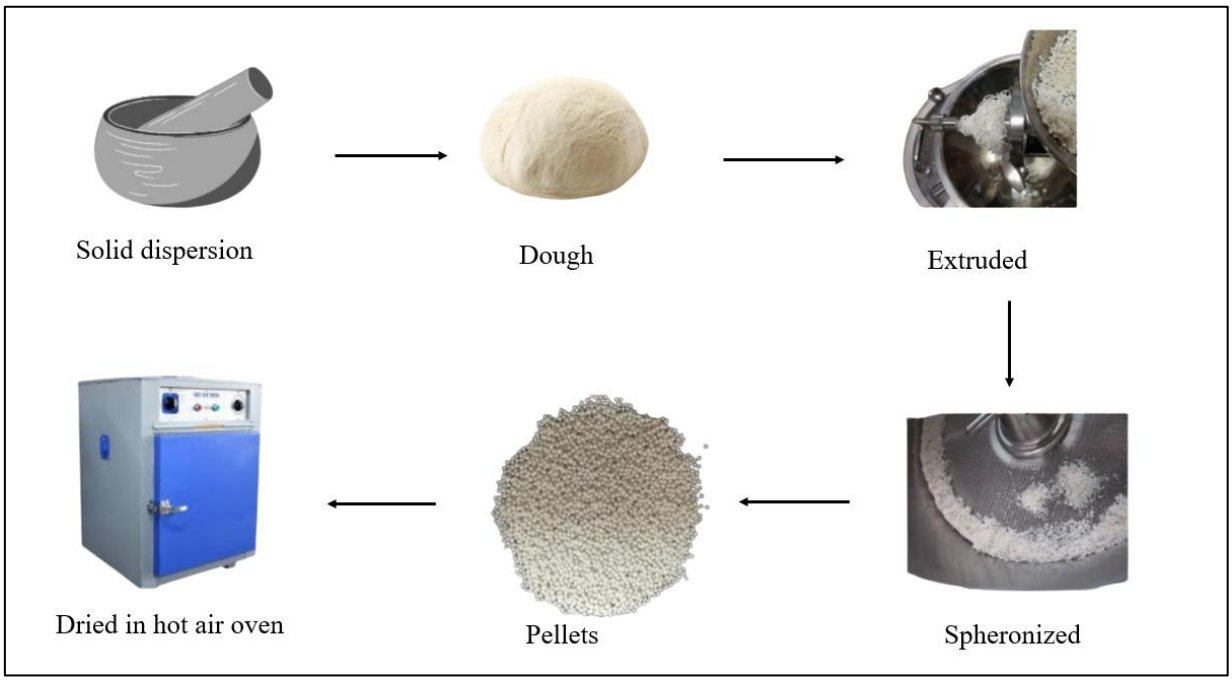
Figure 2: Preparation of pellets



2.4Model Fitting and optimization by experiment design

Table 1: Formulation of immediate release pellets DOE batches with material quantity

Sr. No	Run	Solid Dispersion			MCC (gm)	CCS(mg)
		Drug (mg)	Polymer-1 (mg)	Polymer 2 (mg)		
1	F1	400	400	200	8	200
2	F2	400	400	200	9	200
3	F3	400	400	200	10	200
4	F4	400	400	200	8	300
5	F5	400	400	200	9	300
6	F6	400	400	200	10	300
7	F7	400	400	200	8	400
8	F8	400	400	200	9	400
9	F9	400	400	200	10	400

2.5. Solubility study

2.5.1. Solubility study of MEZ

The solubility of meclizine HclanalysedDistilled water, pH 1.2, methanol, and phosphate buffer 6.8 were all treated with excess of meclizine HCL. The meclizine HCL was weighed and transferred into conical flask which contain 10 ml of media. The content in conical flask was sonicated for 2 hr. at room temperature, then the sample were placed on orbital shaking incubator (Fortuna Technology digital orbital shaker) agitated at room temperature for 48 h. finally the solutions

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were filtered, suitably diluted and analyzed spectroscopic method at λmax 238.5 nm.

2.5.2. Solubility study of drug in solid dispersion
The solubility of solid dispersion analysed in various solvent like Distilled water, pH 1.2, methanol, and phosphate buffer 6.8 were all treated with excess of solid dispersion of meclizine HCL and polymer SoluPlus® and TPGS made using the Solvent Evaporation method. The solid dispersion was weighed and transferred into conical flask which contain 10 ml of media. The content in conical flask was sonicated for 2 hr. at room temperature, then the sample were placed on orbital shaking incubator (Fortuna Technology digital orbital shaker) agitated at room temperature for 48 h. finally the solutions were filtered, suitably diluted and analyzed spectroscopic method at λmax 238.5 nm.

III. Characterization of Solid dispersion and pellets

3.1Attenuated total reflection infrared spectroscopy (ATR-IR)
FTIR spectra of Meclizine Hcl, soluplus, TPGS, solid dispersion, powder pellets were recorded as potassium bromide dispersion on an FTIR spectrometer-430 (Shimadzu 8400S, Tokyo, Japan) at a scanning range 4000–400 cm^{-1} with a 4 cm^{-1} resolution (Sonawane and Patil 2018).

3. 2. Differential scanning calorimetry
Differential scanning calorimetry was used to find the melting point of theMEZ , solid dispersioncontaining drug and both polymers and optimized bath pellets (F7 batch). DSC was used to obtain the thermogram (Mettler DSC 1 star system, Mettler-Toledo, Switzerland). Weighed accurately 2 mg of each sample were analysed in a range of 40-300℃ (heating rate 10℃/min with nitrogen purging rate of 30 mL/min) in aluminum crucibles.

3.3 X-ray power diffractions (XRD)
The x-ray powder diffraction pattern of powdered of the meclizine hcl, soliddispersion , and optimized batch pellets were analysed by X ray diffractometer (X-pert PRO, Panalytical, Netherlands) with glass tubing Cu anode and graphite monochromator at 30 mA and 40 kV,. The sample was put on a glass slide. Over a range of 10-30º diffraction angle (2θ), a rate of 10/min was used.

3.4 Scanning electron microscopy
The surface morphology and topographic characteristics of the formulated Meclizine Hcl pellet were evaluated using a desktop Scanning Electron Microscope (Phenom G6 Pure, Thermo Fisher Scientific, USA). The sample was prepared by mounting a small quantity directly onto a specialized aluminum stub using double-sided adhesive carbon tape. Imaging was conducted without sputter coating, utilizing both the Backscattered Electron Detector (BSD) and the Secondary Electron Detector (SED) to capture high-resolution topographic and compositional surface details. The microscope utilized a long-lifetime Cerium Hexaboride (CeB6) electron source, operating at an accelerating voltage of [5 kV and 10 kV]. The samples were scanned at multiple magnifications to observe particle shape, uniformity, and surface texture. All data acquisition and image processing were performed using the integrated Phenom ProSuite software.

3.5. Flow properties of pellets (Sonawane R.O et al.,2021)
The flow properties of prepared pellets were analyzed by bulk density, tapped density, Hausner's ratio, Carr's compressibility index, and angle of repose.

3.6. Polarized light microscope
The pellet size and shape of the prepared pellets bathes ware determined using polarized light microscopy. The five pellets of each batch of Meclizine pellets were selected and observed under the Leica polarized light microscopes fitted with f-601 camera imaging accessory and 5x magnification size of pellets was observed (Sonawane RO et al., 2017)

3.7. Determination of pellet size, roundness, circularityand aspect ratio
Formulation batches of Meclizine Hcl pellets were evaluated for particle size. The pellets (n=10) were taken for particle size analysis and the average size was determined. Particle size of the pellets was measured using Polarized light microscope fitted with a f-601 camera imaging accessory and using Leica software. The images of pellets were analyzed for their average diameter, perimeter, radius and different shape factors such as roundness and circularity, and also Aspect ratio Aspect ratio is defined as the ratio of the length of a pellet divided by the width, with pellets being considered round (spherical) if the aspect ratio lies between 1.0 and 1.20. The roundness, circularity and Aspect ratio

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values of prepared pellets were determined following equations.

$$\text{Roundness} = \frac{0.9399P^2}{4\pi A} \quad eq\ 1$$

$$\text{Circularity} = \frac{4\pi A}{P^2} \quad \text{eq 2}$$

$$\text{Aspect ratio} = \frac{\text{Length of pellets}}{\text{Width of pellets}} \quad \text{eq 3}$$

Were, as P is the perimeter of the pellets image and A is the area determined by the total number of pixels within the feature. The factor 0.9399 corrects the perimeter for the effect of the corners produced by digitization of the image. A roundness value of 1 corresponds to the image of a perfect sphere.

3.8. Friability of pellets

Accurately 10 grams of weighed matrix pellets were put in the plastic chamber of a Roche Friabilator (Electrolab Friability tester, EF 2) then shocked and abraded for 4 minutes at 25 rpm. The weight of the pellets maintained on the sieve was then measured after the pellets were screened using Tyler's sieve number 24 . The mean of three determinations ± SD percent is used to express the results. Percent Friable amount was calculated using Eq.

$$\%\ \text{Friability} = \frac{Wi - Wf}{Wi} \times 100 \quad eq\ 4$$

$$\text{Circularity} = \frac{4\pi A}{P^2} \quad eq\ 5$$

$$\text{Pellips} = \frac{P}{\pi Dmax} \quad eq\ 6$$

3.9. Percent drug content of pellets

The drug content of pellet formulations were determined in accurately weighed 100 mg pellets. The pellets were powdered in mortar, and the powder is dissolved in methanol using ultra-Sonication. After filtration, the UV absorbance(UV-1700, Shimadzu, Japan) of the suitably diluted filtered through a membrane filter (0.45 µm), was measured at 238 nm to determine the drug content. The content uniformity test was carried out three times for each formulation, and the results were expressed with the standard deviations. (Sonawane and Patil 2018).

3.10. Disintegration test

Tablet disintegration tester DT 2 (ROLEX Tablet disintegration rate test device IP) was used to assess the breakdown of pellet formulations in water. They employed special translucent tubes with a diameter of 10 mm and a length of 15 mm. At the top and bottom of this tube were sieves with a mesh size of 710 mm. Each tube was filled with 100 mg of pellets before being placed in the typical tablet disintegration testing. At a rate of thirty dips, the disintegration time of six dried samples at 37 °C was measured.

3. 11. In- vitro dissolution (Maderuelo et al.,2019)

In-vitro drug release was performed by dissolving MEZ HCl in pellet using a DT-6 USP type I apparatus (Dissolution Tester EDT 08Lx, Electrolab, Mumbai, India) at a basket speed of 50 rpm in 900 ml of pH 1.2 at 37± 0.5 °C for one hour. To maintain the sink condition 5 ml sample was withdrawn at 5, 10, 20, 30, 40, 50 and 60 min intervals and replaced with fresh dissolving medium. The obtained sample was passed through a 0.45 µm membrane filter and the absorbance was recorded at 238 nm using UV spectrophotometer (UV-1700, Shimadzu, Japan) at regular intervals.

3.12. Comparative study

In- vitro dissolution (Maderuelo et al.,2019)

The equivalent dose amount of Meclizine Hcl tablet (Diligan® - 25) was dissolved in 900 ml of pH 1.2 using DT-6 USP type I apparatus (Dissolution Tester EDT 08Lx, Electrolab, Mumbai, India) at 37±0.5 C for one hour. To maintain sink conditions, 5 ml of sample was withdrawn at 10, 20, 30, 40, 50 and 60 minutes and replaced with fresh dissolving medium. The collected sample was filtered through a 0.45 µm membrane filter and absorbance at 238 nm was monitored periodically by using a UV spectrophotometer (UV-1700, Shimadzu, Japan)

Determination of difference and similarity factors.

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Determination of difference and similarity factors (F1 and F2) was calculated by comparing drug release of tablet and optimized batch F4 at time interval of 10 to 60 min by given formula.

IV. Result and discussion

4.1.Solubility study

4.1.1. Solubility study of MEZ

The study of the drug's solubility suggests that the values of solubility depend on pH and solvent. Water solubility was found to be at a relatively low level of 0.023 units. Under acidic conditions (pH 1.2) the solubility increased significantly to 0.194 units which indicate increased solubility compared to neutral pH. Likewise, the solubility with pH 6.8 was still high with 0.187 units. Although water solubility is important and this should be improved if necessary for the best formulation development. It showed a much higher solubility in methanol, 0.720.The results obtained emphasize the effect of type of solvent and pH on the solubility properties of drug. Further studies and possible improvement strategies for aqueous formulations are necessary.

Table 2: Solubility of MEZ in the different solvent

Sr. no.	Solvent	Observed solubility(mg/ml)
1	Water	0.023
2	1.2 pH buffer solution	0.194
3	6.8 pH buffer	0.187
4	Methanol	0.720

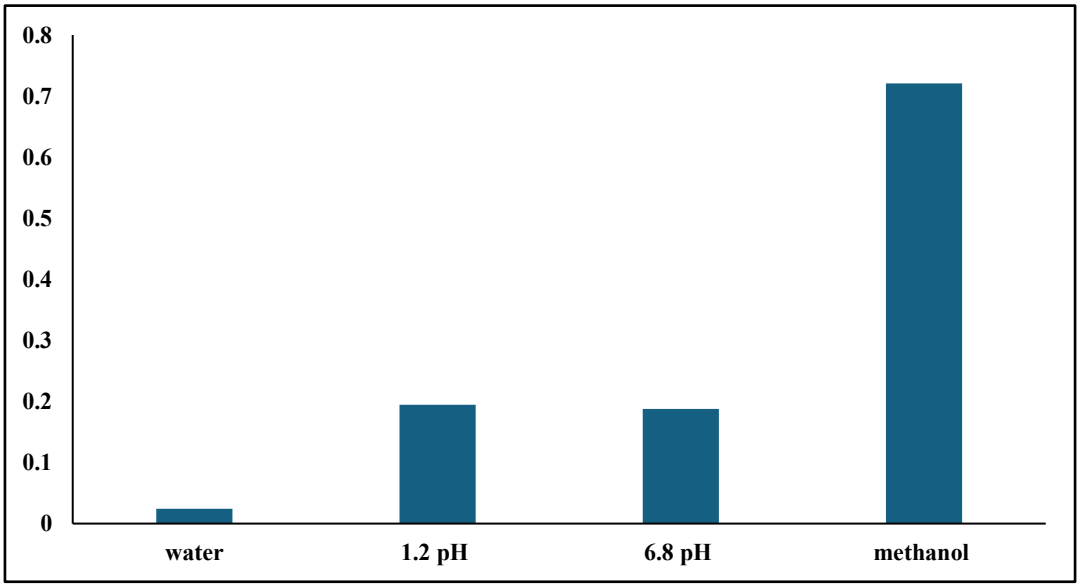

Figure 3: Solubility determination of Meclizine

4.1.2.Solubility study of drug in solid dispersion

Solubility of Meclizine Hydrochloride was studied in different media such as water, methanol, pH 1.2 buffer and pH 6.8 buffer. The solubility of the pure drug was measured first. To enhance the drug solubility, solid dispersions of the drug were prepared with Soluplus and D-α-Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) at different ratios. Solubility of these formulations in selected solvents was studied. The results showed significant increase in solubility of solid dispersions as compared to pure drug. Maximum solubility was observed with the higher polymer ratios (especially 1:1:0.5) in all media, especially in methanol and pH 1.2 buffer among the different formulations. Based on the solubility results, the formulation with the highest solubility was chosen as the optimized ratio and was used for further characterization and evaluation studies.

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Table 3: Solubility study of drug in solid dispersion and polymer with different concentration

Sr. no.	Parameters	Water	1.2 pH buffer solution	6.8 pH buffer solution	Methanol
1	Drug	0.02399	0.19443	0.18771	0.72093
2	SD with soluplus	0.17321	0.2478	0.26338	0.97674
3	SD with TPGS	0.53458	0.63991	0.45061	1.81395
4	1:1:1	0.62181	0.89513	0.7602	2.76744
5	1:1:0.5	0.94579	1.90209	1.68157	3.97674
6	1:1:0.25	0.76199	1.17123	1.19754	3.04651

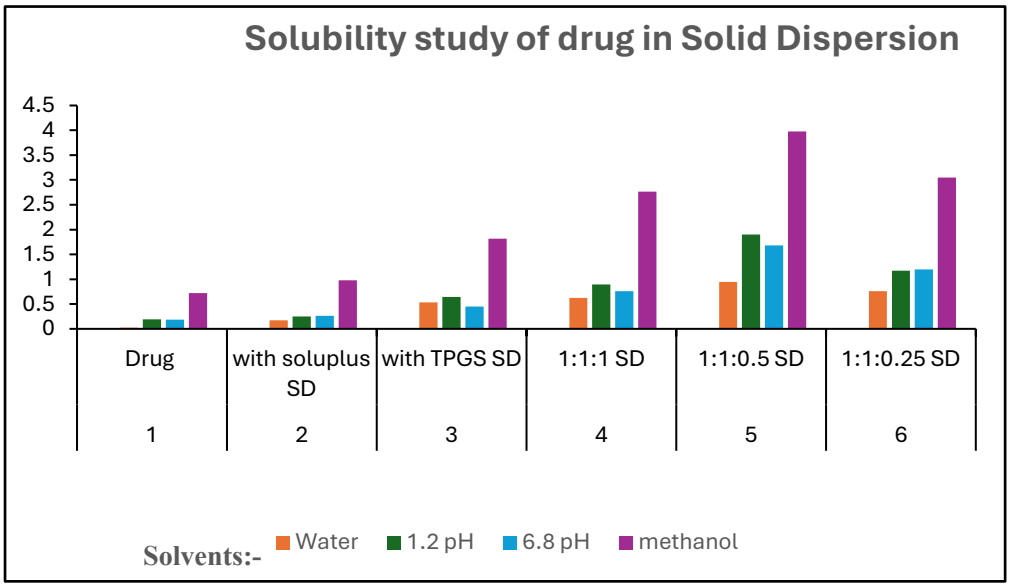

Figure 4: Solubility study of drug in Solid Dispersion

4.2. ATR-IR analysis

The ATR-FTIR spectra observation showed that the solid dispersion and pellet formulation preparation involved successful incorporation of Meclizine Hydrochloride with SoluPlus® and TPGS polymers. It confirmed the presence of characteristic functional groups and compatibility between drug and excipients. The ATR-IR spectrum of Meclizine HCl showed characteristic peaks at 2940-2850 cm-1 corresponding to C-H stretching vibrations, peaks at 1450-1500 cm-1 corresponding to aromatic C=C stretching vibrations and peaks in the region 1100-1000 cm-1 corresponding to C-N stretching vibrations of the drug molecule. The ATR-IR spectrum of SoluPlus® presented characteristic peaks in the region of 2920 cm-1 for aliphatic C-H stretching vibrations, a prominent peak in the region of 1630–1730 cm-1 for the carbonyl (C=O) stretching vibrations and the peaks in the region of 1100–1250 cm-1 were attributed to the C-O stretching vibrations. The ATR-IR spectrum of TPGS showed characteristic peaks at 2880–2920 cm^{-1} corresponding to C–H stretching vibrations and peaks at 1100 cm^{-1} corresponding to ether (C–O–C) stretching vibrations. The ATR-IR spectrum of solid dispersion containing Meclizine HCl, SoluPlus® and TPGS retained major characteristic peaks of drug and polymers with minor shifting and decrease in peak intensity indicating the lack of chemical interaction between drug and carriers. Slight broadening of the peak and reduction in intensity indicated hydrogen bonding and partial conversion of the drug from crystalline to amorphous state in the polymeric matrix. Similarly, ATR-IR spectrum of optimized pellet formulation showed characteristic peaks of Meclizine HCl and polymers with minor shifting and decrease in intensity but no disappearance of principal peaks or appearance of any new peaks was noticed, confirming the stability of the drug during pellet preparation and absence of significant incompatibility between drug and excipients. The ATR-IR study showed successful integration of Meclizine HCl into the polymeric carrier system in general and the compatibility of the drug with SoluPlus® and TPGS. The small widening of the peaks and a fall in their intensity

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indicated a partial amorphization of the drugwhich might be beneficial for a better solubility and dissolution of the final pellet formulation.(Qazi F. et al., 2017)

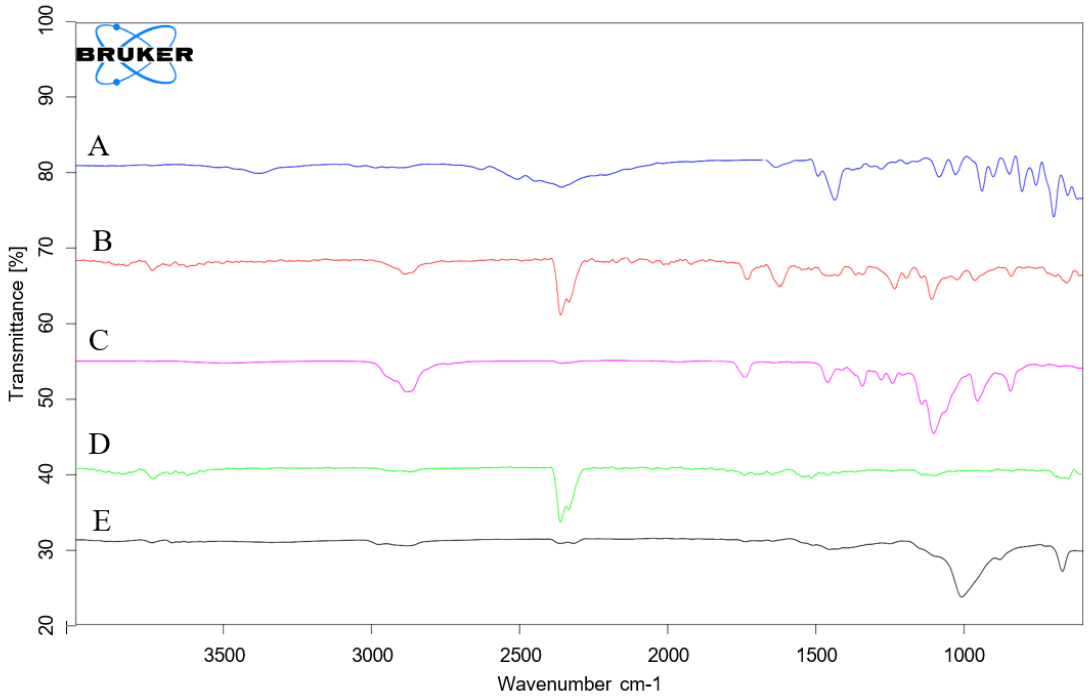

Figure 4: ATR-IR spectra of A-Meclizine Hcl, B-Soluplus, C- TPGS, D- Solid dispersion, E-Pellets

3.3.DSC Studies

The thermal behaviors of drug, solid dispersion and optimized batch pellets were evaluated by DSC. The DSC curve of Mevclizinehclshowsthe sharp endothermic peak at 218-220℃ to its melting point, indicating its crystalline nature. The DSC thermograph of solid dispersion containing the meclizine Hclboth polymers like TPGS and soluplus it shows reduced the intensity and slight shifting of the characteristic drug peak, indicating partial conversion of the drug from crystalline to amorphous form within the polymer matrix. However the theDSC thermograph of optimized bathch pellets formulation shows the further reduction and broadening of melting peak, confirming uniform dispersion of the drug and decreased crystallinity after pelletization. Overall, the DSC study confirmed successful incorporation of Meclizine HCl into the polymeric system and partial amorphization of the drug, which may enhance solubility and dissolution of the optimized pellet formulation (Lee JY et al., 2015, Qazi F. et al., 2017; Kunam V. et al., 2020).

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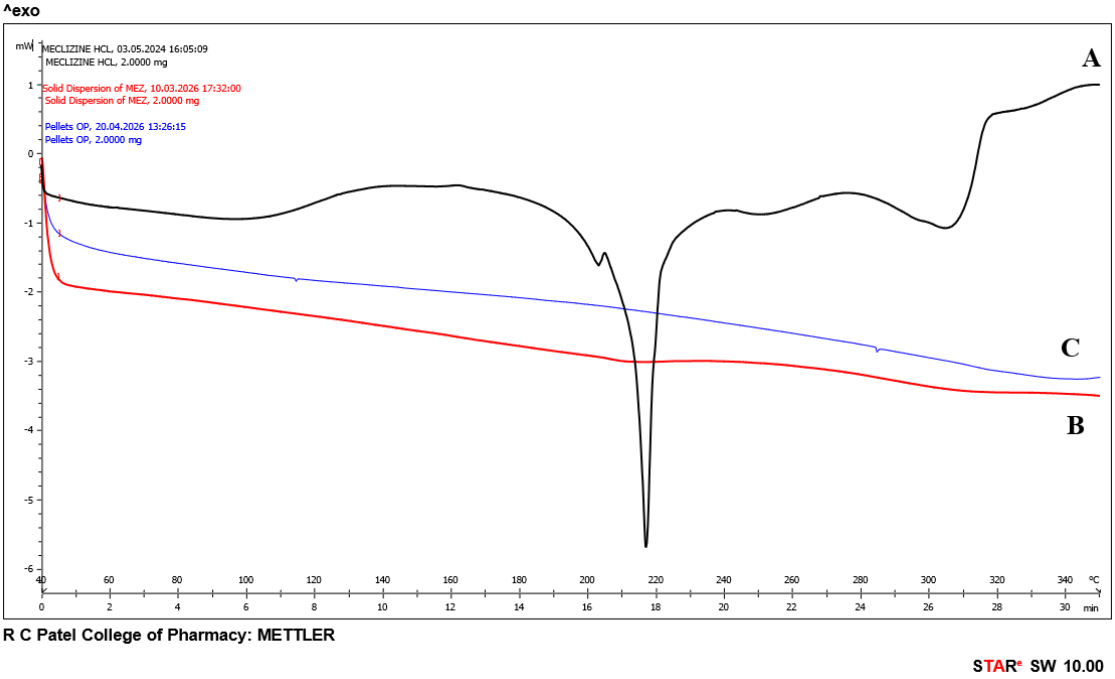

Figure 5: DSC spectra of A-Meclizine Hcl, B-Solid dispersion of meclizine Hcl, C-pellets

4.4. XRPD analysis

The X ray diffraction spectra of meclizine Hcl drug shows the sharp and intense diffraction peaks at 7.629°, 14.936 °, 21.791°, 23.545°, and 26.714° (2θ), confirming its crystalline nature, in the solid dispersion containing meclizine Hcl, soluplus and TPGS the intensity of these characteristic peaks was markedly reduced and converted into broad diffused peaks, with a halo pattern observed mainly in the range of 15–30° (2θ), indicating reduction in crystallinity and partial conversion of the drug into an amorphous form due to molecular dispersion within the polymer matrix. However the XRD pattern of optimized batch pellets shows predominantly broad and diffused peaks with almost complete disappearance of the characteristic crystalline peaks of the drug. A prominent broad halo peak around 20–25° (2θ) confirmed the maintenance of the amorphous state after pelletization.

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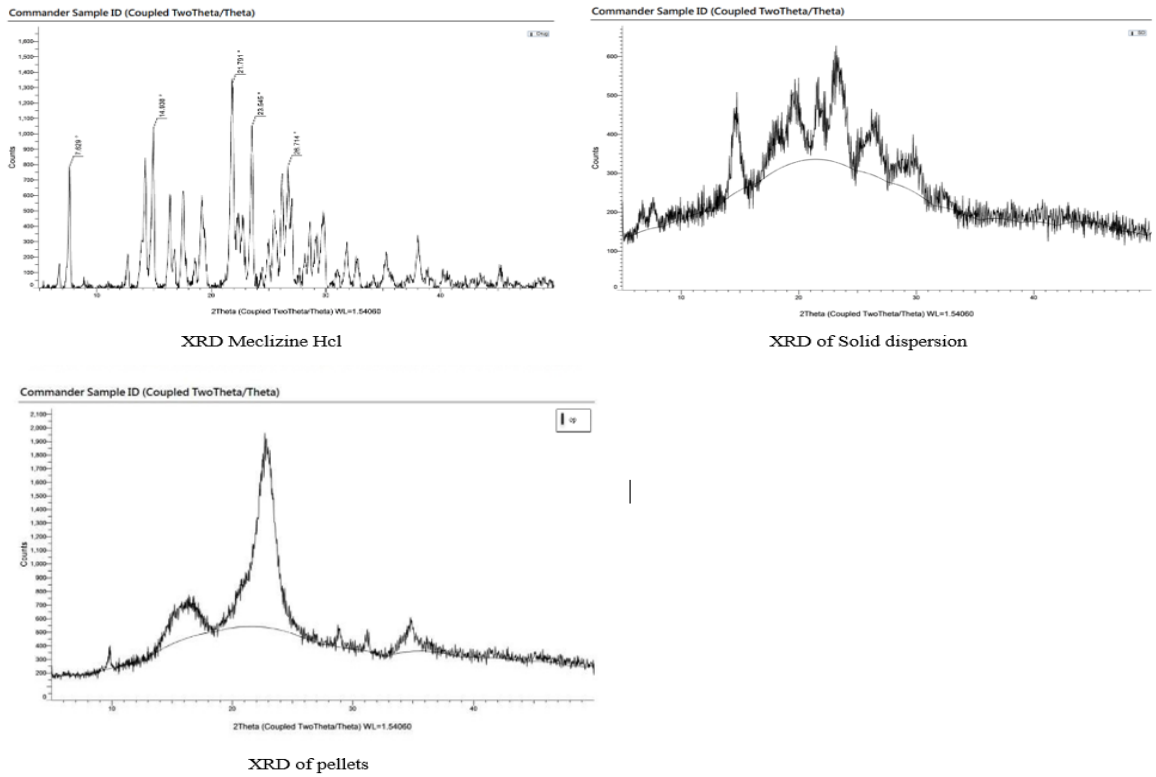

Figure 6: XRD spectra of Meclizine Hcl, solid dispersion, Optimized pellets

4.5. Scanning electron microscopy (SEM)

The scanning electron microscopy (SEM) evaluation is important for determining the surface morphology, size, and shape. SEM images of the formulated pellets at different magnification were shown in **(Figure 7,8).** Surface morphology of pellets studied by SEM indicated that the pellets give oval shape and somewhat rod-shaped pellets with rigid surface.

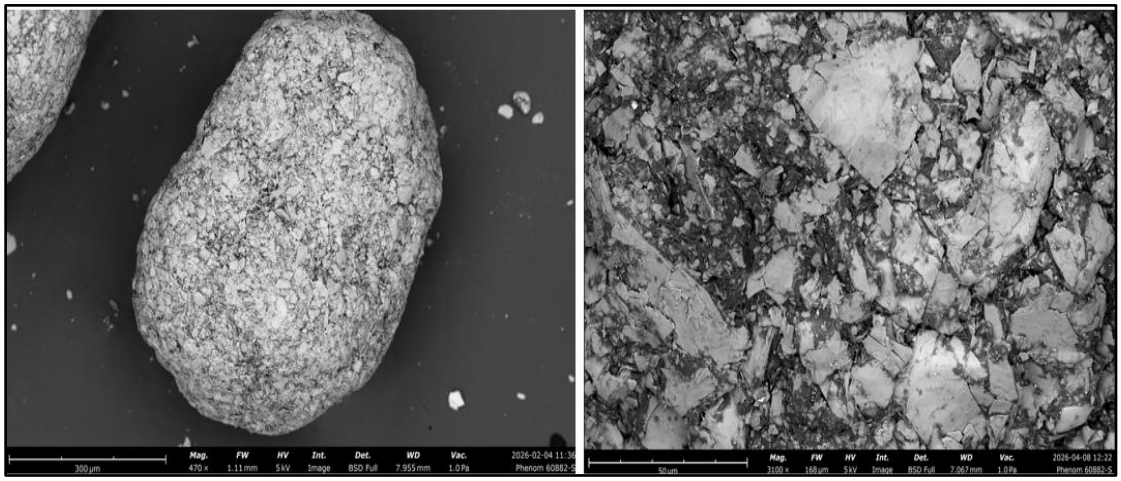

Figure 7: SEM of single pellet 100µm **Figure 8: SEM of single pellet 50 µm**

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4.6. Flow property

The pellet's flow characteristics were assessed. The most crucial factors for packing pellets into the capsule shell were their flow characteristics. The range of the angle of repose values is 27.14 ± 0.9 to 30.46 ± 0.9. The ranges for the bulk and tapped densities are 0.70 ± 0.1 to 0.78 ± 0.1 (g/ml) and 0.75 ± 0.1 to 0.87 ± 0.1 (g/ml), respectively. Excellent pellet flow characteristics are indicated by the angle of repose, Hausner's ratio, and Carr's index values. The flow properties of each batch were assessed. Table 4 displays the results for each batch.

Table 4. Flow properties of formulated batches of pellets.

Batches	Angle of Repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's Ratio (%)
F_1	28.04 ±1.22	0.73± 0.20	0.80 ± 0.18	8.75 ±1.36	1.09 ± 0.33
F_2	29.36 ±1.84	0.74 ± 0.15	0.81± 0.25	8.64 ±1.84	1.09 ± 0.52
F_3	28.00 ±1.42	0.75 ± 0.17	0.82 ± 0.28	8.54 ±1.59	1.09 ± 0.44
F_4	27.81 ± 1.75	0.78 ± 0.16	0.86 ± 0.17	9.30 ±1.57	1.10 ± 0.32
F_5	29.05 ± 1.52	0.72 ± 0.10	0.79 ± 0.21	8.86 ±1.76	1.09 ± 0.25
F_6	29.35 ± 1.20	0.77 ± 0.21	0.84 ± 0.16	8.33 ±1.45	1.09 ± 0.41
F_7	**29.84 ± 1.24**	**0.80 ±0.11**	**0.88 ±0.21**	**9.09 ±1.42**	**1.10 ±0.48**
F_8	30.25 ±1.45	0.79 ± 0.22	0.87 ± 0.20	9.19 ±1.89	1.10 ± 0.56
F_9	29.52 ±1.12	0.76 ± 0.16	0.83 ± 0.10	8.43 ± 1.28	1.10 ± 0.74

4.7. Polarizing-light microscopy of pellets (F1-F9).

The pellets size and shape of the prepared pellets batches were determined by using polarized light microscopy. Formulated 5 selected pellets of each batch were observed in magnification 5X (Fonseca-santos,2017). Characterization of the pellets formulation is performed by using leica polarized microscope equipped with f-601 camera. Polarized light microscopy of formulated pellet batches shows in fig 9.

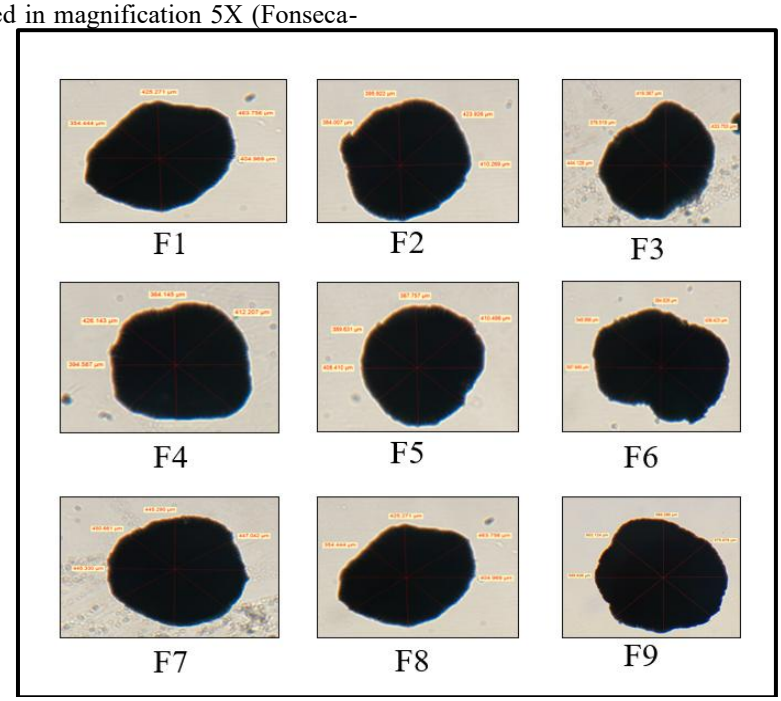

Figure 9: PLM images (F1-F9)

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4.8. Determination of pellet size, roundness, circularityand aspect ratio

Matrix pellets containing Meclizine Hcl were evaluated for particle size. the pellets (n=5) were taken for particle size analysis and then average particle size was determined. Particle size of the pellets was measured using a polarized light microscope fitted with a f-601 camera imaging accessory and using Leica software.

Table 5: Morphological characteristics of batches F1-F9

Formulation	Pellets size (µm)	Roundness	Circularity	Aspect ratio
F1	796.5 ± 25.08	0.94 ± 0.10	0.996 ± 0.12	1.02 ± 0.28
F2	811.6 ± 35.55	0.94 ± 0.17	0.999 ± 0.26	1.02 ± 0.43
F3	828.4 ± 36.60	0.95 ± 0.32	0.996 ± 0.12	1.11 ± 0.23
F4	799.6 ± 38.73	0.94 ± 0.19	0.997 ± 0.13	1.04 ± 0.26
F5	810.5 ± 32.34	0.95 ± 0.27	0.997 ± 0.23	1.03 ± 0.40
F6	829.6 ± 35.85	0.94 ± 0.26	0.996 ± 0.20	1.04 ± 0.42
F7	831.5 ± 25.41	0.95 ± 0.33	0.997 ± 0.17	1.06 ± 0.33
F8	822.5 ± 28.50	0.94 ± 0.19	0.996 ± 0.18	1.08 ± 0.42
F9	859.4 ± 41.57	0.94 ± 0.24	0.999 ± 0.26	1.08 ± 0.24

The particle size analysis, roundness, circularity for all formulation batches is shown in table in table5. Aspect ratio, circularity and roundness are important parameters for characterization of pellets. Aspect ratio nearer to 1 and roundness found in limit and shows the spherical pellets. The particle size of matrix pellets of different batches was found in the range of 0.7 to 0.8 mm (700-800 µm) which matches to standard limit. Hence, it was found that F7 batch showed particle size, aspect ratio and more circularity.

4.9. Friability, drug content of pellets and Disintegration time

The friability was studied in order to determine the mechanical properties of the pellets, the friability of the pellets tested in friability tester was below 1%. The % friability for all batches F1-F9 are found to be in range 0.26 ± 0.11 to 0.34 ± 0.12, and thus the pellets have desirable hardness and of good quality with respect to friability. The preliminary aim to produce mechanically strong pellets with thereby achieved. The drug loaded pellets of Meclizine prepared with optimized formula exhibited drug loading capacity in range of 88% - 96%.Disintegration time within 4-8 min as it is a immediate releaseShown in table 6.

Table 6: Friability, Percent Drug content of formulation batches F1-F9

Formulation	% Friability	% Drug contain	Disintegration time (min)
F1	0.28 ± 0.08	88.43 ± 0.5	5.2 ± 3.5
F2	0.34 ± 0.12	90.02 ± 0.9	5.8 ± 1.1
F3	0.29 ±0.12	93.19 ± 1.5	6.1 ± 0.8
F4	0.30 ± 0.14	91.15 ± 1.1	5.2 ± 6.2
F5	0.32 ± 0.12	94.53 ± 0.8	5.5 ± 1.1
F6	0.35 ±0.10	93.65 ± 1.8	5.9 ± 1.5
F7	0.27 ±0.09	96.82 ± 0.8	4.6 ± 0.9
F8	0.33 ±0.10	91.60 ± 0.9	4.9 ± 0.8
F9	0.26 ± 0.11	92.06 ± 1.1	5.8 ± 1.8

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4.10. In- vitro dissolution

In vitro drug release was studied in USP type I apparatus containing 900 ml of 1.2 pH buffer at 37± 0.50C and agitated at a speed of 50 rpm. The profile and dissolution data of the formulations F1–F9 at pH 1.2 are shown in Figure 10. The dissolution profile showed the %CDR of batches F1 to F9 in the range of 79.20% to 96.42% at the end of 60 minutes. From the above discussion, it can be concluded that batch F7 showed the highest drug release of about 96.42% at the end of 60 minutes in comparison with the other batches.

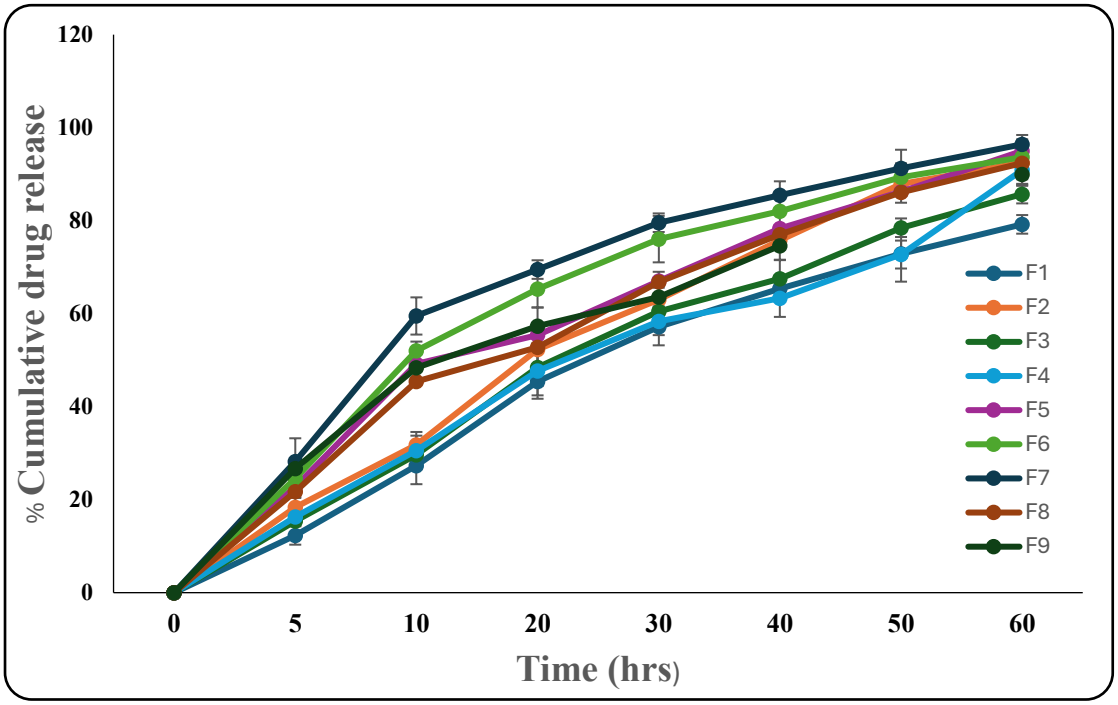

Figure 10: Cumulative drug release of (F1-F9)

3.11. Comparative study

4.11.1. In- vitro dissolution

Using a USP type I apparatus, an in-vitro drug release investigation was conducted in 900 ml of 1.2 pH buffer at 37 ± 0.5^0C with a stirring at speed of 50 rpm. Figure 11 displayed the dissolution results and profile of formulation F7 and tablet Diligan®-25 in pH 1.2. According to the dissolving profile, the percentage CDR of batch F7 was found to be between 28.2% and 96.42% after 60 minutes, whereas tablet Diligan®-25 was found to be between 20.56% and 91.12%. Based on the discussion above, it can be determined that, after 60 minutes, batch F7 had the largest drug release of around 96.42%, whereas tablet Diligan® 25 had a drug release of approximately 91.12%.

4.11.2. Determine of difference and similarity factors.

Similarity and difference factor (F1and F2) was calculated (table 7) from that it was concluded that there is no significant difference in both formulation as all the values reported were in the acceptable range.

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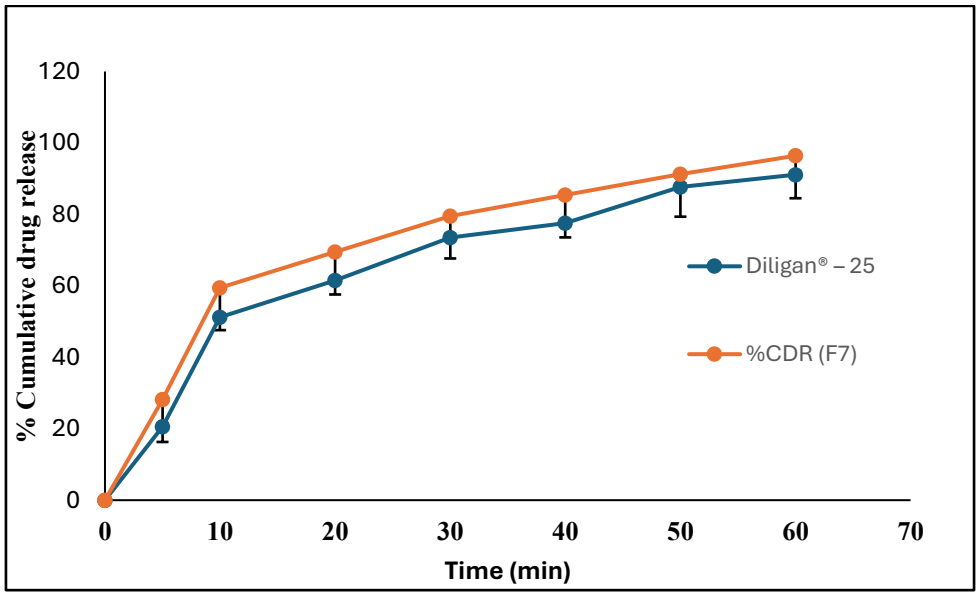

Figure 11:%Cumulative Drug Release F7 vs Tab Diligan®-25

Table 7: Difference Factor (F_1) & Similarity Factor (F_2)

Product name	**Batch/ lot no.**	**MFG Date**	**Exp. Date**	**MFG By**	
Diligan®- 25					
Difference Factor (F1) & Similarity Factor (F2) In 1.2 pH					
Time (min)	Reference (Diligan®- 25)	Test (F7)	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
0	0	0	0.00	0.00	0.00
5	20.56	28.2	-7.64	58.37	7.64
10	51.2	59.5	- 8.30	68.89	8.30
20	61.52	69.48	-7.96	63.36	7.96
30	73.56	79.56	-6.00	36.00	6.00
40	77.59	85.46	-7.87	61.94	7.87
50	87.68	91.25	-3.57	12.74	3.57
60	91.12	96.42	-5.30	28.09	5.30
Sum	463.23			242.93	33.70
Number of Time or intervals (Excluding Zero)					5
Difference Factor - F_1 [Acceptance Criteria: 0 - 15]					7.28
Similarity Factor - F_2 [Acceptance Criteria: 50 - 100]					57.62

4.12.Model optimization and data analysis

Based on a 3^2 complete factorial design applying Design Expert® Version 13.0.0 (Stat-Ease Inc., Minneapolis, USA), a methodical formulation design technique was used to create an optimal immediate-release formulation of meclizine Hcl pellets. The research aim to determine how three dependent variables Y1 = Pellet Size, Y2 = % Cumulative Drug Release (%CDR), and Y3 = Disintegration Time—were affected by two independent variables: the amount of Microcrystalline Cellulose (MCC, coded as factor A) and Croscarmellose sodium (CCS, coded as factor B).

The extrusion-spheronization procedure was used to prepared the pellets. Nine experimental runs (F1–F9) were produced by the 3^2factorial design, which made it possible to estimate linear, interaction, and quadratic effects. The chosen formulation factors were examined at Low, medium, and high are the three levels. Mathematical models were created to predict response values after the collected data was statistically examined using ANOVA to assess the importance of model terms.

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Regression Equations for Dependent Variable

Equation 1 (Y1-Pellet size): $Y1=+821.44+16.90*A+27.19*B-0.0561*AB-13.10*A^2-5.42*B^2$ ——————————————————————————— $eq\ 7$

Equation 2 (Y2-% Drug release): $Y2=+96.36+0.3675*A+3.18*B-3.39*AB-4.79*A^2-3.56*B^2$ ——————————————————————————— $eq\ 8$

Equation 3 (Y3-Disintegration time): $Y3=+5.48+0.4876*A-0.2938*B+0.0564*AB-0.0163*A^2-0.06.5*B^2$ ——————————————————————————— $eq\ 9$

Both MCC (A) and CCS (B) have a considerable impact on the responses, according to the derived equations for Y1 (pellet size), Y2 (% drug release), and Y3 (disintegration time). Pellet size increases with increasing MCC and CCS, with CCS having a greater impact. CCS primarily increases drug release, whereas higher MCC somewhat restricts it and their interaction at high levels decreases release. Disintegration time lowers with CCS because of its dissolving activity, but it increases with MCC because of matrix formation. These effects are supported by the response surface plots, which also show an ideal area at moderate MCC and CCS levels. The result mainly considered % drug release, and the plot provided the optimized amount of 8 g of MCC and 400 mg of CCS in the formulation, which gave the best suitable results. Finally, it was concluded that formulation batch F7 was the optimized formulation among all batches.

Table 8. The values of regression analysis and ANOVA for measured responses for dependent variables.

Response	Model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Summary of results of regression analysis for measured responses						
Y1	Quadratic	0.7947	0.6921	0.3839	16.22	2.02
Y2	Quadratic	0.8384	0.7576	0.5653	2.68	2.96
Y3	Quadratic	0.9725	0.9587	0.8653	0.1035	1.91
Parameter	SS	DF	MS	F-Value	p-value	Significance
Summary of results of ANOVA for measurement responses						
Pellets size						
Model	10178.90	5	2035.78	7.74	0.0032	Significant
Residual	2629.41	10	262.94	-	-	-
Cor total	12808.31	15	-	-	-	-
% Drug release						
Model	371.76	5	74.35	10.38	0.0010	Significant
Residual	71.64	10	7.16	-	-	-
Cor total	443.40	15	-	-	-	-
Disintegration time						
Model	3.79	5	0.7574	70.64	< 0.0001	Significant
Residual	0.1072	10	0.0107	-	-	-
Cor total	3.89	15	-	-	-	-

R2 , coefficient of regression; SD, standard deviation; CV, coefficient of variance, SS, sum of squares; DF, degree of freedom; MS, mean sum of squares; F, Fisher's ratio.

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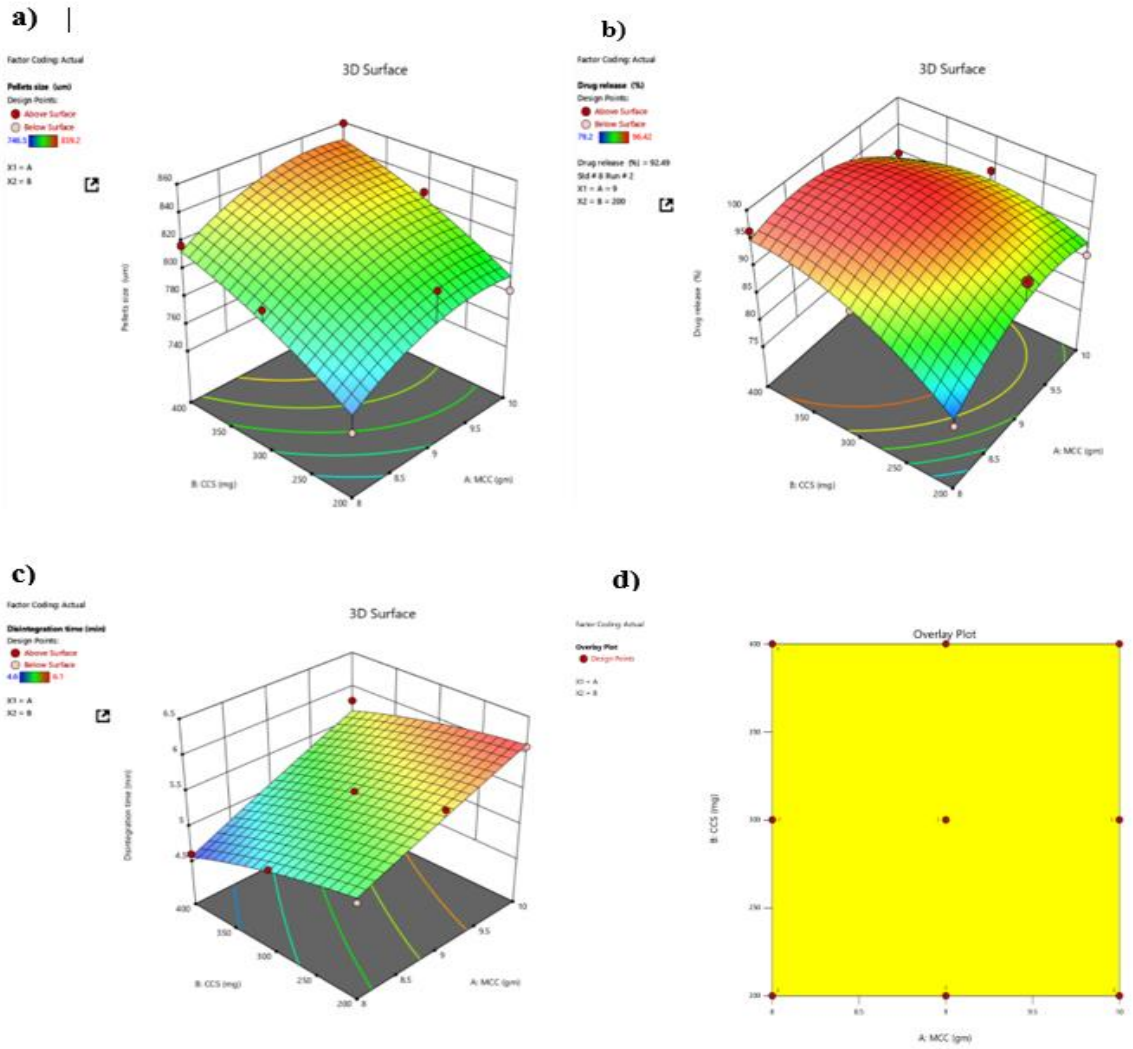

Figure 12: Response surface plots showing influence of MCC(A) and κ-carrageenan concentration (B) on (a) pellet size (Y1), (b) % drug release (Y2), (c) Disintegration time (Y3), (d) overlay plot.

V. Conclusion

Our study concludes by highlighting the promising potential of SoluPlus® and TPGS polymer-formulated immediate release pellets to improve MEZ solubility. Improved quick drug release properties were made possible by the addition of croscarmellose sodium. In addition, the pellets showed ideal mechanical stability, size, shape, and flow characteristics, and no polymer contact was detected. Over a duration of 60 minutes, batch F7 showed excellent immediate drug release patterns. As a result, the drug's solubility was improved by the use ofSoluPlus® and TPGS polymer, and its rapid release was facilitated by the disintegrant Croscarmellose sodium.

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