RESEARCH ARTICLE

Superporous Hydrogels as Super Disintegrants in Formulating Oral Disintegrating Tablets of Clozapine for the Treatment of Schizophrenia

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ABSTRACT

In this study, clozapine was formulated as orally disintegrating tablets (ODTs) using a direct compression method, incorporating super porous hydrogels as superdisintegrants. The disintegration time, hardness, friability, and stability of these ODT formulations were systematically evaluated, along with detailed dissolution profiles. Surprisingly, friability measurements revealed values below 1%. All tablet formulations disintegrated completely within 1 minute, meeting the 3-minute disintegration time criterion specified by the USP for ODTs. Moreover, over 85% of the labeled clozapine content was dissolved within 15 minutes from the ODTs. FTIR analysis indicated no interaction or alterations between the active ingredient and excipients. Consequently, the ODT formulations prepared using super porous hydrogels as superdisintegrants represent a promising strategy. This approach could significantly aid in the development and manufacturing of generic clozapine products.

Keywords: Clozapine, Superporous hydrogels, Oral disintegrating tablets, USP.

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INTRODUCTION

Oral disintegrating tablets, or ODTs, are gaining popularity within the pharmaceutical sector since they disintegrate in the mouth and do not need water to aid swallowing. This new dosage form has potential advantages across all age groups, including youngsters, the elderly, and individuals with schizophrenia who have trouble engulfing regular tablets or capsules.[1] The quick breakdown of the tablet is caused by the rapid absorption of water into its matrix.[2-5]

For fast disintegration, choosing the right type and amount of disintegrant is crucial.[5] In FDT formulations, sodium croscarmellose and sodium starch glycolate have been utilized as wicking agents.[6-8] It was recently discovered that superporous hydrogel (SPH) with fast swelling and superabsorbent properties could be used for the development of a gastric retention device. Hydrogels with open channel structures are called SPHs. The absorption of water into the dried SPHs occurs through capillary wetting, in contrast to diffusion. The dried SPH hydrogels exhibit an exceptional rate of swelling, with the swelling ratio potentially exceeding 100-fold within minutes.[9,10]

SPH microparticles, characterized by their unique porous structure, facilitate rapid water transport through capillary forces, leading to an exceptionally swift wicking effect into the tablet's core. It is hypothesized that tablets compressed directly with SPH microparticles will disintegrate at an accelerated rate due to the quick absorption of water into the tablet's core.[11] To assess the impact of the microparticles on the disintegration of tablets, FDTs with model drug clozapine using SPH as a disintegrant are developed.

MATERIALS AND METHODS

Acrylic acid, acrylamide, chitosan, BIS, and TEMED were acquired from SRL Chem (Pvt. Ltd), Maharashtra, India; Clozapine was bought as a gift sample from SS Pharma Labs Pvt. Ltd., Hyderabad. AC-Di-Sol, Aspartame, Mannitol SD 200, Microcrystalline cellulose, magnesium stearate, sodium starch glycolate and sucrose were acquired from Signet Excipients Pvt. Ltd. S.D. Fine Chem. Ltd., Mumbai, was the supplier of Span 80, ammonium persulphate, and sodium bicarbonate. The solvents, reagents, and extra compounds all utilized were of the analytical variety.

Methods

Compatibility study

By using FTIR spectra from a Perkin Elmer Spectrum I, it was possible to determine whether the pure drug and excipients were compatible. Solid samples were prepared using the

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potassium bromide pellet method, while liquid samples were put in a liquid cell and their spectra were recorded between 4000 and 500 cm^{-1}.

Differential scanning calorimetry studies (DSC)

DSC (DSC 60, Shimadzu, Japan) was used to record the thermograms of both pure drug and blend. At a heating frequency of 10°C per minute, the measurement was carried out between 30 and 350°F.

Formulation of superporous hydrogels (Table 1)

First, a 6% chitosan solution with 5% glacial acetic acid was made. This chitosan solution—which can also be added as powder—was introduced to the beaker along with Ac-Di-Sol. Acrylamide, acrylic acid, BIS, Span 80, APS, TEMED, and drug were added to the aforesaid solution/powder while stirring. After that, polymerization was allowed to go for ten minutes. Lastly, the above-mentioned solution was rapidly mixed with sodium bicarbonate, and stirring was done for the required amount of time. SPHs were cut to the appropriate size and heated for 48 hours to dry them out.[12]

Evaluation of Superporous Hydrogels

Mechanical strength

The SPH and their composites were tested for mechanical characteristics using a bench comparator. Positioned longitudinally below the lower touch of a bench comparator attached to a micrometer gauge was a sample swelled in simulated stomach fluid (SGF). There was a lab jack supporting the Superporous hydrogel. The bench comparator's upper touch received weights placed on it incrementally. Using the gauge, the Superporous hydrogel's swelling height under pressure was determined. The mass and the lower touch's contact area were used to compute the pressure that was imparted to the Superporous hydrogel. To describe the mechanical features of the Superporous hydrogels, two metrics were identified: ultimate compression pressure (UCP) and swelling height below 100 cm water pressure. Applying weights in increasing amounts until the Superporous hydrogel began to shatter allowed researchers to calculate the UCP.[13]

Porosity and density of the hydrogels

After measuring the hydrogel films' porosity in a 20 mL beaker, the mass of the empty beaker (W1) was determined. Cyclohexane, an inert solvent, was gradually added to the beaker after up to 1 g of hydrogel film had been introduced. After that, the beaker's weight (W2) was determined. Subsequently, the hydrogel sheets were extracted and quantified (W3). The pore volume of the hydrogel films was determined by measuring the amount of cyclohexane present in each pore of the hydrogel films. The following formulae were used to determine the porous gel's (P) porosity:

$$P = Vp/Vp + Vg \quad (4)$$

where

- Vg is the volume of the hydrogel (cm^3), and
- Vp is the volume of cyclohexane in the pore (cm^3).[14]

Drug content

A beaker was filled with precisely weighed hydrogel (100 mg), and 20 mL of 0.1N HCl, and the mixture was well mixed before being clarified through Whatman filter paper No. 1. Next, 10 mL of volumetric flask capacity was filled with 1.0 mL of the filtered solution, and 10 mL of 0.1N HCl was added to the volume. Using a UV spectrophotometer, this solution was examined.

Formulation of oral disintegrating tablets

The primary excipients that were chosen were mannitol, sucrose, and cellulose. Aspartame was employed as a sweetener and magnesium stearate as a lubricant. Sodium starch glycolate and super porous hydrogel formulations (CSH4 & CSH8) were employed as superdisintegrants. All of these excipients were completely combined with 25 mg of clozapine for 10 minutes to form 100 mg tablets, which were then compressed using a 5 mm punch by a Kalweka Rotary tablet compression machine. Table 2 lists the ODT formulations of clozapine along with their components.

Evaluation of Mini-Tablets

Pre-compression

The flow property of the blend was assessed before compression by evaluating its bulk density, tapped density, angle of repose, compressibility index, and Hausners ratio following USP General chapter <1174>.[15]

Post-compression:

The resulting USP general chapters, Weight Variation & Drug Content <905> within a limit of [NLT 90%- NMT 110%],

Table 1: Preparation of SPH

S.No	*Ingredient*	*CSH1*	*CSH2*	*CSH3*	*CSH4*	*CSH5*	*CSH6*	*CSH7*	*CSH8*
1	Chitosan 6% (mL)	2	4	6	8	-	-	-	-
2	Ac-Di-Sol (gms)	-	-	-	-	0.120	0.240	0.360	0.480
2	Acrylamide 50% (mL)	3	3	3	3	3	3	3	3
3	Acrylic acid 50% (mL)	2	2	2	2	2	2	2	2
4	BIS 2.5% (mL)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
5	Span 10% (mL)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
6	APS 20% (mL)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	TEMED 16.7% (mL)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	Sodium bicarbonate 20% (mL)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table 2: Formulation of oral disintegrating tablets of clozapine by SPH

S. No	*Ingredient (mg)*	*CF1*	*CF2*	*CF3*	*CF4*	*CF5*	*CF6*	*CF7*	*CF8*	*CF9*
1	Clozapine	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
2	Sodium Starch Glycolate	2.0	4.0	6.0	-	-	-	-	-	-
2	SPH-CSH4-(Chitosan)	-	-	-	2.0	4.0	6.0	-	-	-
3	SPH-CSH8-(AC-Di-Sol)	-	-	-	-	-	-	2.0	4.0	6.0
4	Mannitol	48.0	46.0	44.0	48.0	46.0	44.0	48.0	46.0	44.0
5	Microcrystalline Cellulose	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
6	Sucrose	13.0	13.0	13.0	13.0	13.0	13.0	13.0	13.0	13.0
7	Aspartame	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
8	Magnesium Stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Tablet weight		100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Hardness, Thickness & Friability <1217>, were consulted for the evaluation of compressed tablets' post compression parameters.[16–24]

In-vitro disintegration time

Using the USP Lab India Disintegration apparatus without a disc, the disintegration time of the six ODTs was measured at a frequency of 30 ± 2 cycles/min, and 1000 mL of water was maintained at 37 ± 2°C.

In-vitro drug release study

The protocol described in the Clozapine USFDA dissolution database was followed. Using USP type II apparatus, 4.5 pH phosphate buffer, 900 mL, 50 RPM, 37 ± 5°C, and 30 minutes as the dissolution conditions, oral disintegrating tablets were evaluated for drug release from the formulation at 5, 10-, 15-, 20-, and 30-minute sampling intervals. By using a UV-visible spectrophotometer set at 296 nm, samples were acquired.[25]

Stability studies

The stability investigations were conducted per the ICH standards Q1A (R2) for the optimal formulation, suggesting storing conditions at 40 ± 2°C/75% RH ± 5% RH.[26,27]

RESULTS AND DISCUSSION

Compatibility Study by FTIR

The drug's FTIR spectrum did not significantly vary from the Formulation mixture's spectrum, as Figures 1-3 illustrates.

Clozapine infrared spectrum displays a large peak at 3296.86 cm^{-1}, which might be caused by N-H stretching; 3010.01 cm^{-1} could be produced by aromatic C-H stretching; 2969 cm^{-1} could be caused by aliphatic C-H stretching; 1594.13 cm^{-1} could be caused by amidine C=N stretching; 1433.52 cm^{-1} could be caused by Aromatic C=C stretching; 1047.13 cm^{-1} could be caused by aromatic C-Cl stretching. The drug's IR spectrum was interpreted using the formulation combination and each excipient separately, and it was found that the positions of the distinctive bands did not significantly alter. It is possible to deduce that the drug retains its individuality without enduring any chemical interactions with the additives employed in the formulation.

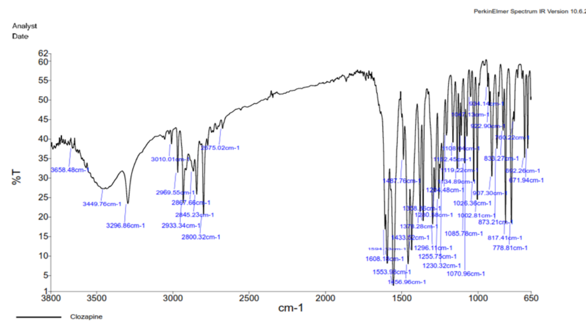

Figure 1: FTIR spectra of clozapine

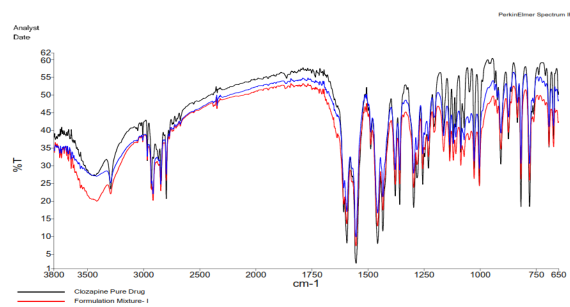

Figure 2: Spectral overlay of clozapine pure drug along with mixture I containing (Chitosan) and mixture II containing (AC-Di-Sol).

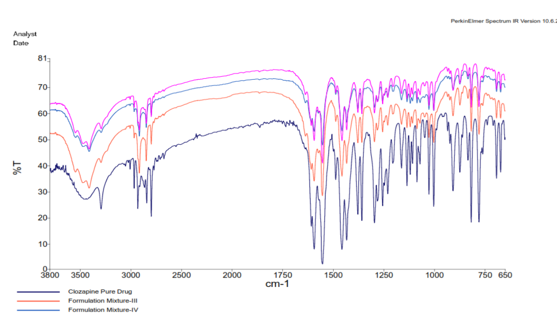

Figure 3: Spectral overlay of clozapine pure drug along with mixture III containing (SSG), mixture IV containing (SPH-Chitosan) & mixture V containing (SPH-AC-Di-Sol)

Table 3: Evaluation of superporous hydrogel formulation

Formulations	*Drug content (%)*	*Density*	*%Porosity*	*Mechanical strength (cm water pressure)*
	88.17	1.106	45.8	188.12
CSH1	89.56	0.74	24.53	200.23
	98.23	1.379	29.02	205.38
Average	91.99	1.075	33.12	197.91
	91.23	1.075	39.19	238.15
CSH2	88.45	1.496	37.87	267.89
	89.11	1.038	33.26	218.36
Average	89.60	1.203	36.77	241.47
CSH3	92.87	1.339	75.98	382.65
	89.29	1.736	61.67	334.22
	90.22	1.014	68.44	313.39
Average	90.79	1.363	68.70	253.43
	89.56	0.98	67.92	412.65
CSH4	91.43	1.37	51.21	444.12
	89.87	1.479	58.48	385.56
Average	90.29	1.276	59.20	414.11
	98.42	1.89	78.12	512.56
CSH5	97.67	1.529	75.64	550.17
	98.12	1.646	73.12	534.81
Average	98.07	1.688	75.63	532.51
	94.58	1.608	84.39	631.42
CSH6	97.12	2.272	89.18	643.19
	95.36	1.708	86.36	662.84
Average	96.28	1.863	86.64	645.82
	89.45	2.715	78.28	652.29
CSH7	92.51	2.342	82.53	623.67
	90.11	1.712	79.81	639.22
Average	92.09	2.256	80.21	638.39
	94.32	2.655	91.29	639.12
CSH8	97.89	3.136	88.62	658.38
	95.27	2.397	84.77	641.76
Average	94.89	2.729	88.23	646.42

Evaluation of Superporous Hydrogels

The hydrogels underwent a rigorous preparation process and were evaluated for their mechanical strength, porosity, density, and drug content. It was observed that as the quantity of polymer chitosan and Ac-Di-Sol increased, the density, percentage porosity, and UCP values also saw a corresponding increase. However, it was noted that there was not a proportional increase in UCP with the higher quantity of polymer. This discrepancy could be attributed to the enhanced water absorption capacity of the polymer, which may lead to a weakening of the SPH structure. The results, as illustrated in Table 3, suggest that the density, percentage porosity, and mechanical strength of the formulations prepared with Ac-Di-Sol were found to be satisfactory in comparison to those prepared with chitosan. Drug content was found within the range of (89.60–98.07%). CSH4 & CSH8 were considered optimized formulations based on mechanical strength & porosity.

Evaluation of Clozapine Oral Disintegrating Tablets

According to the pharmacopoeial restrictions, the results showed acceptable bounds and favorable flow characteristics for every compound.

Friability and weight variation results shown in Table 4 were determined to be within acceptable limits. The measurements of thickness and hardness were taken, revealing a range of 2.65-2.97 mm, 74.62-85,42 N for hardness, and 98.28-102.44% for drug content. The prepared tablets dissolved in 20.2 and 59.8 seconds, meeting the pharmacopeia-recommended disintegration time of 3 minutes for Oro dispersible tablets.

Formulations prepared with super porous hydrogels as superdisintegrants using AC-Di-Sol as a property modifier/ composite agent showed reliable disintegration time. According to this study, ODTs containing 6% Ac-Di-Sol superdisintegrant had a shorter disintegration time than ODTs containing 2% Ac-Di-Sol. In high concentrations, Ac-Di-Sol's fiber structure allows for water wicking in both intraparticular and extraarticular modes, causing it to swell dramatically when put in contact with water.

Study of *In-vitro* Drug Release

From the dissolution data obtained above, it has been observed that an increase in the concentration of super disintegrating agent increased the dissolution rate (Figure 4). According to the USP monograph, the Q point for an orally disintegrating tablet is not less than 85% at the end of 15 minutes. Formulation containing super porous hydrogel as super disintegrants has shown rapid drug release in comparison to the commercial grades of superdisintegrants available in the market. Formulation (CF9) was considered the optimized formulation, as it showed rapid drug release (85.29%) at the end of 15 minutes (Tables 5 and 6).

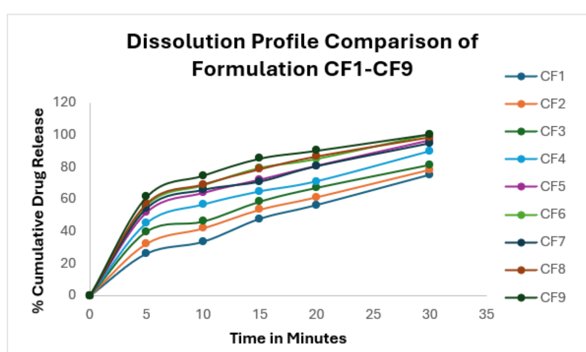

Figure 4: Dissolution profile comparison of clozapine oral disintegrating tablet formulations (CF1-CF9)

Table 4: Post-compression evaluation parameters for clozapine oral disintegrating tablets

Formulation	*Weight variation (mg)*	*Thickness (mm)*	*Hardness (N)*	*Friability (%)*	*Drug content (%)*	*Disintegration time (s)*
CF1	98.00	2.73	85.42	0.18	101.34	59.8
CF2	103.22	2.85	81.33	0.20	99.16	48.4
CF3	100.92	2.74	84.60	0.26	102.44	42.8
CF4	99.93	2.65	79.68	0.41	98.28	47.3
CF5	100.67	2.97	80.24	0.22	100.11	38.2
CF6	97.85	2.83	82.86	0.19	99.62	32.9
CF7	100.54	2.92	78.12	0.28	102.12	33.1
CF8	102.43	2.89	74.62	0.38	99.56	26.8
CF9	99.21	2.78	75.24	0.41	98.45	20.2

Table 5: *In-vitro* drug release data of clozapine ODT

Dissolution (Minutes)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	26.16	32.34	39.89	45.20	51.76	56.09	54.48	57.20	61.40
10	33.50	41.85	46.14	56.71	63.83	68.58	65.97	69.21	74.70
15	47.72	53.44	58.52	64.88	72.08	79.35	71.15	78.63	85.29
20	56.28	61.20	67.08	71.15	80.66	84.92	80.70	86.54	90.18
30	75.07	78.31	81.41	89.86	96.50	100.18	95.05	98.48	100.43

Table 6: Stability studies of optimized clozapine oral disintegrating tablets

Dissolution time (Minutes)	*CF9-optimized at 40 ± 2°C/75 RH ± 5% RH*	
	Initial	*After 3 months*
	%Cumulative drug release	
0	0	0
5	61.40	63.26
10	74.70	71.51
15	85.29	85.90
20	90.18	89.55
30	100.43	99.92
Average drug content (%)	98.45	97.82

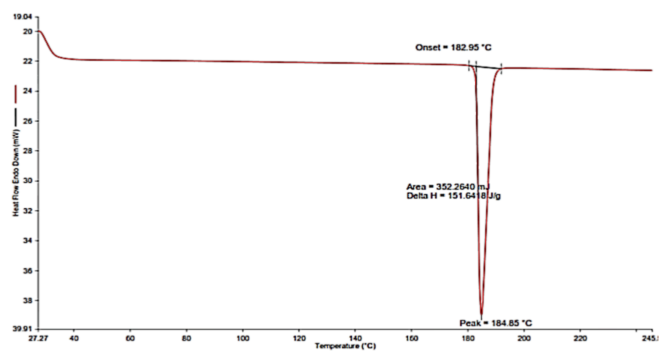

Figure 6: DSC spectra of the clozapine oral disintegrating tablet optimized formulation (CF9-O) before stability

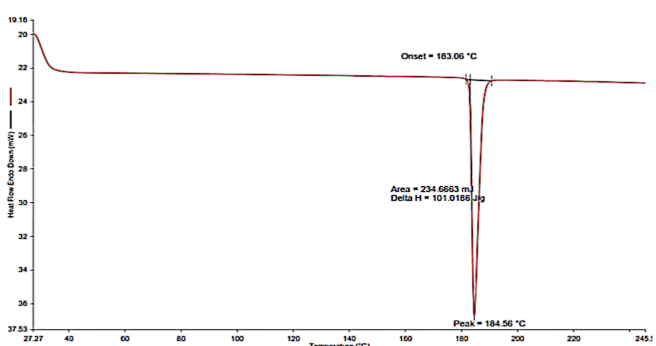

Figure 5: DSC spectra of the clozapine oral disintegrating tablet optimized formulation (CF9-O) before stability

Stability Studies

For the optimized formulation (CF9-Optimized), short-term accelerated stability tests showed that all were found to be in satisfactory bounds. As a result, the formulation is considered stable.

DSC

The DSC spectrum of CF9-optimized was shown in Figures 5 and 6 both before and after stability experiments. Clozapine endothermic peak values were recorded at 183.06°C before stabilization and 182.95°C following stability. The DSC spectrum indicated that none of the examined substances exhibited any potential interaction or deterioration.

Conclusion

The size of microparticles in SPH significantly influenced the disintegration time of oral disintegrating tablets. The findings suggest that AC-Di-Sol-based SPH microparticles exhibit promising super disintegrant properties for the formulation of ODT.

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