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Effect of Different Stabilizers on Spherical Agglomerates of Montelukast Sodium by Quasi Emulsion Solvent Diffusion (QESD)

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Abstract: ***The present study was focused on the spherical crystallization of an asthmatic drug, Montelukast Sodium (MLS) using quasi emulsion solvent diffusion (QESD) technique in which distilled water was an external phase and the internal phase consisted of Ethanol which acts as good solvent and Ethyl acetate as a bridging liquid for recrystallization and agglomeration process. Apart from being poorly water soluble, MLS exhibits poor flow and compressibility. The spherical agglomeration was carried out in the presence of different stabilizers like acacia, PEG 4000, sodium lauryl sulphate, span 40 and tween 80. The prepared agglomerates were characterized in terms of production yield, drug content, solubility,*** **in-vitro** ***release profile, X-ray diffraction (XRD), and Fourier transform infra red spectroscopy (FT-IR).The optimized spherical agglomerates exhibited excellent physicochemical and micromeritic properties, solubility and dissolution rate when compared with pure drug .The XRD also revealed a characteristic decrease in crystallinity. The dissolution studies demonstrated a marked increase in the dissolution rate. FTIR study reveals there are no chemical changes in prepared recrystallized agglomerates. The considerable improvement in the dissolution rate of MLS from optimized crystal formulation was attributed to the wetting effect of polymers, decreased drug crystallinity, altered surface morphology and micronization. If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed spherical agglomerates with improving the physicochemical and micromeritic properties.***

Keywords: Agglomeration, Crystallization, Montelukast Sodium, Quasi Emulsion Solovent Diffusion (QESD), Spherical agglomerates.

I. INTRODUCTION

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low production costs. To be absorbed into the systemic circulation after oral delivery, a medication must first be dissolved in gastric juices. The dissolving process is the rate-controlling phase for hydrophobic medicines, determining the rate and degree of absorption. As a result, many hydrophobic medicines exhibit inconsistent and inadequate absorption in both animals and humans. As a result, poor solubility is one of the biggest obstacles to drug development today, with an estimated 40% of all newly discovered medications being weakly soluble or insoluble in water.[1] Furthermore, due to their high lipophilicity, up to 50% of orally delivered medicinal compounds have formulation issues.[2] As a result, extensive research has been performed to improve medication solubility and dissolution rates in order to boost the oral bioavailability of hydrophobic medicines. One method for improving dissolution is to reduce particle size and/or increase saturation solubility. Milling, a mechanical micronization technique, is one of the most prevalent methods for reducing particle size. Milling is a well-established technology that is relatively inexpensive, quick, and simple to scale up. However, milling has various drawbacks, the most significant of which is the restricted ability to control essential features of the finished particle such as size, shape, morphology, surface properties, and electrostatic charge. Furthermore, milling is a high-energy procedure that disrupts the drug's crystal structure, resulting in the presence of disordered or amorphous regions in the final product.[3] Because these amorphous regions are thermodynamically unstable, they are prone to recrystallization during storage, especially in hot and humid circumstances.[4]

The modification of surface characteristics affects the milled product's saturation solubility, as well as its blending and flow properties, which has an impact on the formulation process. Furthermore, milled particles frequently exhibit aggregation and agglomeration, resulting in poor wettability and consequently poor dissolution[5]. An alternative to milling is to grow the particle from a solution to the appropriate size range under controlled conditions, such as spray drying, quasi emulsion solvent diffusion[6] and supercritical fluid technologies.[7,8]

One of the advantages of these methods is the possibility of designing in certain beneficial characteristics such as enhancing dissolution rate by incorporating different polymers. The spherical crystallisation technique has been successfully applied these days to improve the micromeritic properties of drug substances.[9] In the most common case, this technique is reputed to improve the wettability and dissolution rates of different drugs.[10] Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release.[11]

There are two main methods for spherical crystallization: spherical agglomeration (SA method) and quasi-emulsion solvent diffusion (QESD method). In the SA method, a quasi-saturated solution of the drug in a solvent in which it is very soluble is poured into a poor solvent of the drug. Provided that the good and poor solvents are freely miscible and the interaction (binding force) between the solvents is stronger than the drug interaction with the good solvent, crystals precipitate immediately. A suitable amount of a third solvent, which is not miscible with the poor solvent and which preferentially wets the precipitated crystals, is added to the system while stirring. This third solvent, which is called a 'bridging liquid', can collect the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid. When the interaction between the drug and the good solvent is stronger than that between the good and poor solvents, the good solvent drug solution is dispersed in the poor solvent, producing quasi-emulsion droplets, even if the solvents are normally miscible. This is due to an increase in the interfacial tension between good and poor solvents. Then the good solvent diffuses gradually out of the emulsion droplet into the poor solvent phase. The counterdiffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent. This process is known as the quasi-emulsion solvent diffusion (QESD) process.[12]

The objective of this work was to evaluate the feasibility of the quasi-emulsion solvent diffusion technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug, Montelukast Sodium. Moreover, Montelukast Sodium (a BCS class 2 drug) is poorly soluble in water. This work is focused primarily on evaluating the solvent diffusion technique on a lab scale for improving the solubility and dissolution characteristics of Montelukast Sodium. In addition, it also evaluates the effect of different stabilizers on solubility and dissolution rate. The *in vitro* release of the drug from the prepared agglomerated crystals was investigated and compared to that of the pure crystals. A microscopy study was used to study the surface characteristics of the granules. Furthermore, X-ray powder diffraction was utilized to investigate the crystallinity of the system.[13]

II. MATERIALS AND METHODS

A. *Materials*

Montelukast Sodium was obtained from Yarrow Chem Products, Mumbai. Ethanol and Ethyl acetate were obtained from Rankem Chemicals Pvt. Ltd. Acacia (Loba chemie Pvt. Ltd, Mumbai), Polyethylene glycol 4000 (Molychem, Mumbai), Sodium lauryl sulphate (Rankem Chemicals Pvt. Ltd.), Span 40 and Tween 80 were obtained from Thomas Baker Chemicals Pvt. Ltd, Mumbai.

B. *Methods*

All spherical agglomerates were prepared by the Quasi Emulsion Solvent Diffusion method. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The codes of spherical agglomerated crystals of Montelukast sodium with different stabilizers was given in Table 1 and drug, stabilizers composition was given in Table 2. Montelukast sodium (1.0g) was dissolved in good solvent Ethanol (25.0ml).The bridging liquid Ethyl acetate (12.5ml) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (62.5ml) containing different stabilizer like acacia, Tween 80, Span 40, sodium lauryl sulphate, and polyethylene glycol (PEG 4000) with a stirring rate of 500 RPM using magnetic stirrer at room temperature. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through whatman filter paper no.42. The same filtrate was used for subsequent washings of agglomerates. Then agglomerates were dried at 37^0C for 24 hours in a hot air oven.

TABLE 1: Codes Of Spherical Agglomerated Crystals Of Montelukast Sodium With Different Stabilizers

S.NO	STABILIZERS USED	SPHERICAL AGGLOMERATED CRYSTALS CODE
1	No Stabilizer	MLS-SA
2	Acacia	MLS-SA-ACACIA
3	Polyethylene glycol 4000	MLS-SA-PEG 4000
4	Sodium Lauryl Sulphate	MLS-SA-SLS
5	Span 40	MLS-SA-SPAN 40
6	Tween 80	MLS-SA-TWEEN 80

*MLS-SA – Montelukast Sodium – Spherical Agglomerates

Table 2: Composition Of Montelukast Sodium Spherical Agglomerated Crystals

INGREDIENTS	MLS-SA	MLS-SA-ACACIA	MLS-SA-PEG 4000	MLS-SA-SLS	MLS-SA-SPAN 40	MLS-SA-TWEEN 80
Montelukast Sodium	1gm	1gm	1gm	1gm	1gm	1gm
Acacia	-	1gm	-	-	-	-
Polyethylene glycol 4000	-	-	1gm	-	-	-
Sodium lauryl sulphate	-	-	-	1gm	-	-
Span 40	-	-	-	-	1gm	-
Tween 80	-	-	-	-	-	1gm
Ethanol	25ml	25ml	25ml	25ml	25ml	25ml
Ethyl acetate	12.5ml	12.5ml	12.5ml	12.5ml	12.5ml	12.5ml
Distilled Water	62.5ml	62.5ml	62.5ml	62.5ml	62.5ml	62.5ml

C. Particle Size Determination

Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide. About 50 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula,

Average size = (sum of all particle sizes) / (number of particles).

D. Drug Content

The percentage drug content in spherical agglomerates was estimated by dissolving spherical agglomerates equivalent to 100 mg of Montelukast sodium in ethanol, mixing thoroughly by shaking, and making the volume up to the mark within a 6.8 pH phosphate buffer. The solution was filtered, the filtrate was diluted suitably with a 6.8 pH phosphate buffer, and absorbance was measured at 289 nm using a UV/visible spectrophotometer.

E. Percentage Yield

The percentage yield of spherical agglomerated crystals of Montelukast sodium prepared with the quasi emulsion solvent diffusion with three solvents method was determined by using the following equation:

Percentage yield = Practical yield (SA) / Theoretical weight × 100

F. Saturation Solubility Studies

Montelukast sodium spherical agglomerate saturation solubility was determined in triplicate using the saturation solubility method. Excess amounts of SA were added to 10 ml of phosphate buffer with a pH of 6.8 in glass vials. The contents of the vials were vigorously mixed for 30 minutes before further solutions were mechanically shaken to equilibrate. Each vial's contents were centrifuged for 10 minutes at 2500 rpm after 72 hours. The supernatant of each vial was filtered through 0.45µ membrane filter, and the filtrate was diluted suitably with solvent separately. Monteluksat sodium concentration was determined using a double-beam UV-visible spectrophotometer (UV1800, Shimadzu, Japan) at 289 nm in comparison to a blank.

G. Dissolution Studies

In-vitro dissolution studies of spherical agglomerates were carried out for 60 minutes using the USP Dissolution test apparatus type I (Lab India DISSO 2000, eight stages) at 50 rpm. Spherical agglomerates equivalent to 50 mg of Montelukast sodium was used for dissolution study at 37±0.50^{o}C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 1 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 289 nm UV/Visible spectrophotometer.

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III. CHARACTERIZATION OF PREPARED SPHERICAL AGGLOMERATED CRYSTALS

A. Microscopical Study

The prepared agglomerated crystals of Montelukast sodium was spread on the glass slide using a glass rod. Formation of spherical agglomerated crystals of Montelukast sodium was confirmed by examining the prepared agglomerated crystals under an amscope microscope with the magnification power of 45X.

B. Melting Point Determination

Prepared agglomerated crystals of Montelukast sodium melting point was determined by placing a small amount of sample in a capillary tube that was closed at one end and placed in a melting point apparatus. The melting point was noted in triplicate and the average value was noted.

C. FT-IR (Fourier Transform Infrared Spectroscopy) Studies

FT-IR spectra of prepared spherical agglomerates were recorded on a Shimadzu FT-IR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). The potassium bromide pellet method was employed, and background spectra were collected under identical conditions. Each spectrum was derived from single average scans collected in the region 400–4000 cm^{-1}

D. Powder X-Ray Diffraction Studies

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer for the samples using Ni filtered CuK(α) radiation (intensity ratio(α1/α2): 0.500), a voltage of 40 KV, a current of 30 mA and receiving slit of 0.2 inches. The samples were analyzed over 2 theta range of 5-70^o with scanning step size of 0.020^o (2 theta) and scan step time of one second.

IV. RESULTS AND DISCUSSION

All spherical agglomerates were obtained by the quasi- emulsion solvent diffusion method using distilled water as an external phase. The internal phase consisted of Ethanol which acts as good solvent and Ethyl acetate as bridging liquid for recrystallization and agglomeration process.

A. Microscopical Study

Formation of spherical agglomerated crystals was confirmed by examining the prepared drug agglomerates under an Amscope microscope with the magnification power of 45X and observes the morphology. The microscopy images are shown in Figure 1.
Microscopical images of developed drug agglomerates of Montelukast sodium demonstrate that tiny spheres of Montelukast sodium were detected in MLS-SA and MLS-SA-ACACIA. It also demonstrated that MLS-SA-TWEEN 80 and MLS-SA-PEG 4000 have distinct spheres of Montelukast sodium. Microscopical images of MLS-SA-SPAN 40 and MLS-SA-SLS indicate broken clump masses of Montelukast sodium drug spheres.

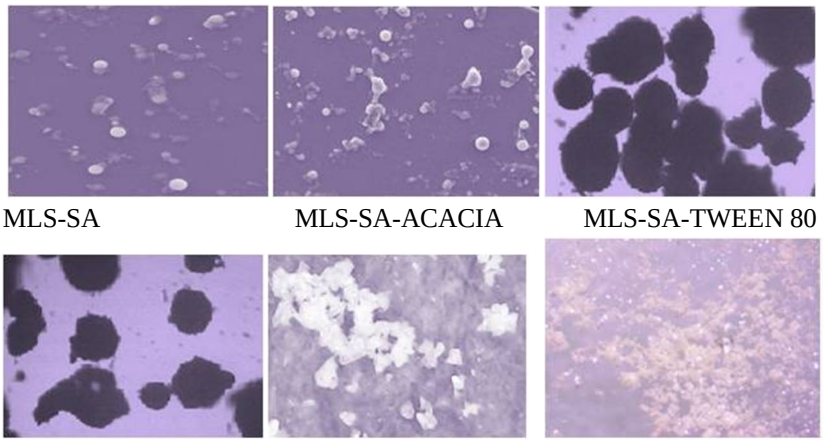

Figure 1: Microscopical Images Of Prepared Drug Agglomerates

B. Percentage Yield, Drug Content And Particle Size

The percentage yield was found among the different formulations of the spherical agglomerated crystals and ranged from 88.49% to 94.24%. The percentage of drug content was found among the different formulations of the spherical agglomerated crystals and ranged from 91.2% to 98.2%. Formulation MLS-SA-PEG 4000 showed a high percentage of drug content (98.2%) and percentage yield (94.24%) compared with all other formulations.

The presence of stabilizers in spherical agglomerates influenced the particle size of resultant agglomerates. As the concentration of the increased, the size of the agglomerates increased. The presence of stabilizers on the particle surface increases particle–particle interaction, causing faster squeezing out of Ethanol to the Surface, resulting in increased particle size. The particle sizes were ranging from 107µm to 235µm in all the prepared spherical agglomerated crystals of Montelukast sodium. Formulation MLS-SA-PEG 4000 showed a large particle size (234.64) compared with all other formulations. This showed that all formulations have uniform particle size distribution.

The percentage yield, drug content and particle size of different formulations of the spherical agglomerated crystals are listed in Table 3.

TABLE 3: Percentage Yield, Drug Content And Particle Size Of Different Formulations Of The Spherical Agglomerated Crystals

S.NO	SPHERICAL AGGLOMERATED CRYSTALS CODE	Percentage Yield (%)	Percentage Drug Content (%)	Average Particle Size (µm)
1	MLS-SA	89.34±0.086	93.6±0.112	107.69
2	MLS-SA-ACACIA	89.96±0.113	91.2±0.045	112.12
3	MLS-SA-PEG 4000	94.24±0.132	98.2±0.094	234.64
4	MLS-SA-SLS	91.41±0.049	96.2±0.098	179.46
5	MLS-SA-SPAN 40	88.49±0.045	89.8±0.065	163.55
6	MLS-SA-TWEEN 80	90.81±0.029	92.2±0.041	217.07

C. FT-IR (Fourier Transform Infrared Spectroscopy) Studies

The IR spectra of pure drug and all the samples are given in Figure 2 and 3. The prominent IR peaks (Wave numbers, cm^{-1}) of drug and prepared spherical agglomerates are given in Table 4. The IR spectra of all the tested samples showed the prominent characterizing peaks of pure Montelukast Sodium which confirm that no chemical modification of the drug has been taken place.

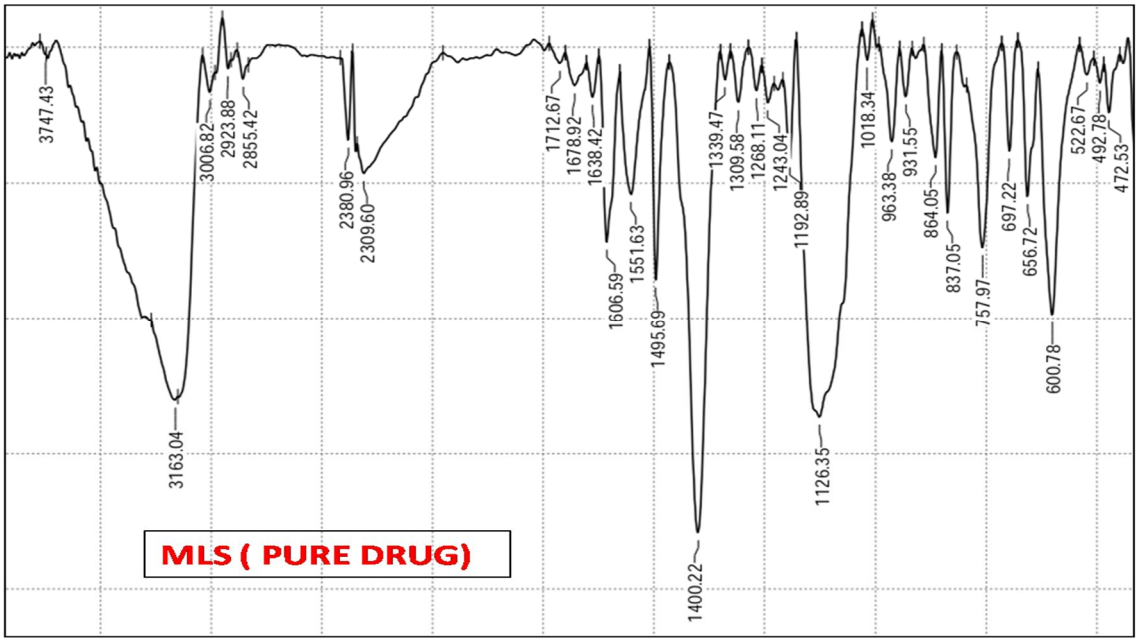

Figure 2: FT-IR Pattern Of Pure Montelukast Sodium

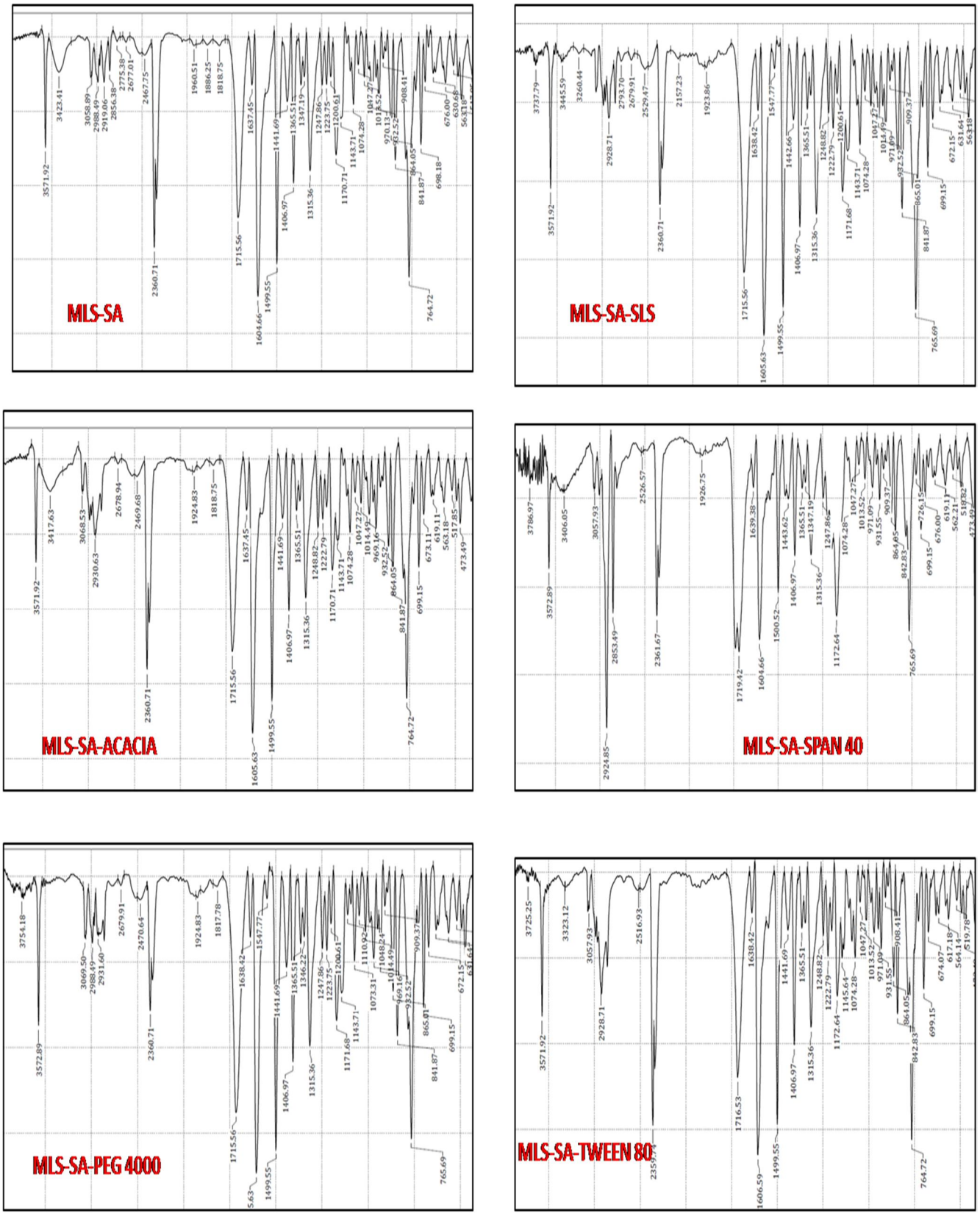

FIGURE 3: FT-IR Patterns Of Spherical Agglomerated Crystals

TABLE 4: FT-IR Peaks (WAVE NUMBERS IN CM^{-1}) OF drug and prepared spherical agglomerates

S.NO	FUNCTIONAL GROUP	Wave Number (cm^{-1})						
		PURE DRUG	MLS-SA	MLS-SA-ACACIA	MLS-SA-PEG 4000	MLS-SA-SLS	MLS-SA-SPAN 40	MLS-SA-TWEEN 80
1	C-H Aromatic	3006	3058	3068	3069	2928	3057	3075
2	O-C-O Stretching	2360	2360	2360	2360	2360	2361	2359
3	C=O Stretching	1712	1715	1715	1715	1715	1719	1716
4	C=N Stretching	1638	1637	1637	1638	1638	1639	1638
5	C=C Stretching	1606	1604	1605	1605	1605	1604	1606
6	Aromatic Ring	1495	1499	1499	1499	1499	1500	1499
7	C-N Stretching	1309	1315	1315	1315	1315	1315	1315
8	C-O Stretching	1192	1170	1170	1171	1171	1172	1172
9	C-Cl Stretching	757	764	764	765	764	764	764
10	C-S Stretching	697	698	699	699	699	699	699

D. Saturation Solubility Studies

The results of solubility study (Table 5) revealed that the spherical agglomerates with different stabilizers showed increased solubility compared to the pure drug. This may be due to the improved porosity, decreased primary particle size and partial amorphization of drug in agglomerates as demonstrated XRD studies. This may also be due to the improved wettability of spherical agglomerates in the presence of stabilizers.

TABLE 5: Saturation Solubility Of Prepared Spherical Agglomerated Crystals Of Montelukast Sodium

S.NO	SPHERICAL AGGLOMERATED CRYSTALS CODE	SOLUBILITY (mg/ml)
1	PURE DRUG	0.9125
2	MLS-SA	1.0882
3	MLS-SA-ACACIA	3.8529
4	MLS-SA-PEG 4000	7.2059
5	MLS-SA-SLS	4.7353
6	MLS-SA-SPAN 40	4.0588
7	MLS-SA-TWEEN 80	5.0941

E. Powder X-Ray Diffraction Studies

The XRD scan of plain Montelukast Sodium showed intense peaks of crystallinity, whereas the XRD pattern of the agglomerates exhibited halo pattern with less intense and denser peaks compared to pure montelukast sodium are given in Figure 4 and 5 indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form. This less intense peak could be due to the increasing the wettability of SA. These results could explain the observed enhancement of solubility and dissolution of Montelukast sodium in spherical agglomeration.

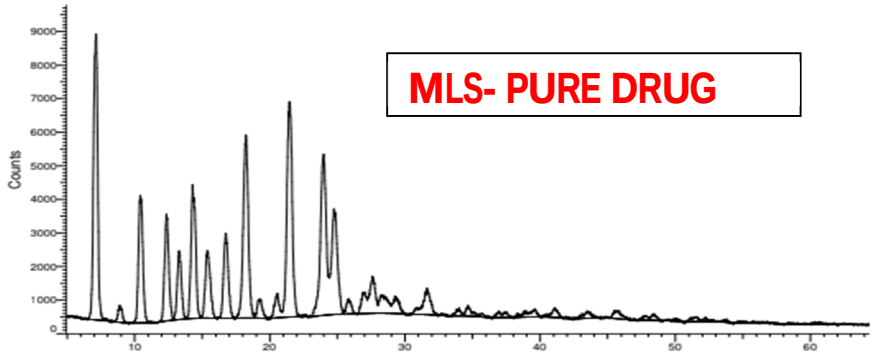

FIGURE 4: XRD Pattern Of Pure Montelukast Sodium

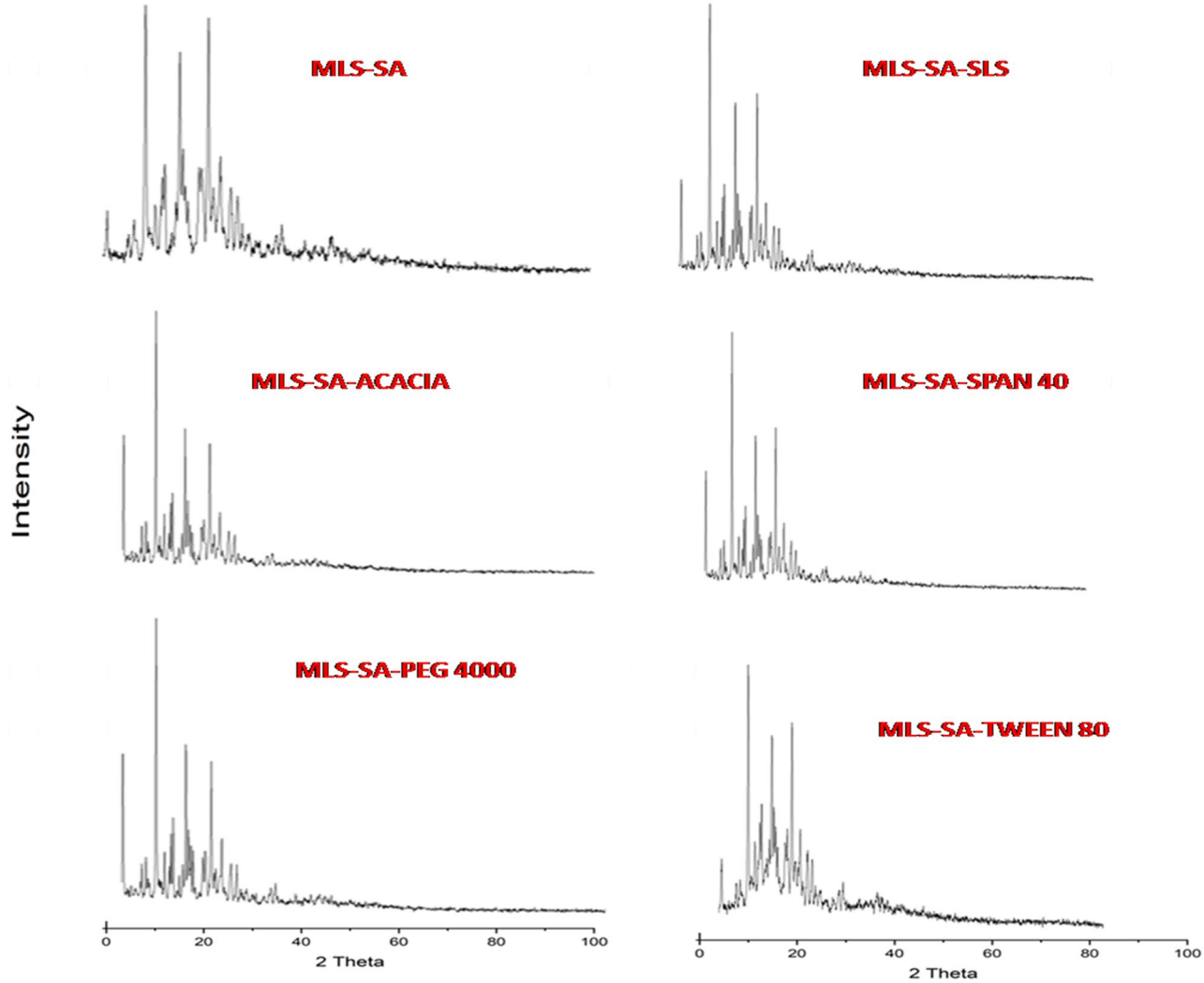

FIGURE 5: XRD Patterns Of Spherical Agglomerated Crystals

F. Dissolution Studies

The *in vitro* drug release of Montelukast sodium spherical agglomerated crystals was shown in Table 6 and Figure 6. The drug release was found among the different formulations of the spherical agglomerated crystals of Montelukast sodium and it was ranged from 63.80% to 91.38%. Formulation MLS-SA-PEG 4000 showed a high percentage of drug release (91.38%) compared with all other formulations.

TABLE 6: In Vitro Drug Release Of Prepared Spherical Agglomerated Crystals Of Montelukast Sodium

S.NO	TIME IN MINS	PERCENTAGE DRUG RELEASE (%)					
		MLS-SA	MLS-SA-ACACIA	MLS-SA-PEG 4000	MLS-SA-SLS	MLS-SA-SPAN 40	MLS-SA-TWEEN 80
1	10	23.21±0.021	29.34±0.081	36.99±0.077	33.17±0.016	26.27±0.044	35.08±0.011
2	20	33.93±0.026	39.68±0.011	53.46±0.012	43.51±0.002	36.61±0.054	45.04±0.022
3	30	42.74±0.034	48.10±0.015	63.80±0.065	55.76±0.012	45.80±0.077	56.53±0.055
4	40	50.78±0.076	59.21±0.056	71.46±0.081	65.72±0.077	53.46±0.011	68.02±0.068
5	50	55.76±0.064	66.49±0.044	84.10±0.013	75.68±0.011	61.12±0.003	78.36±0.097
6	60	63.80±0.069	74.53±0.022	91.38±0.029	81.80±0.021	68.4±0.055	84.49±0.088

*All values are expressed as mean±SD, n=3

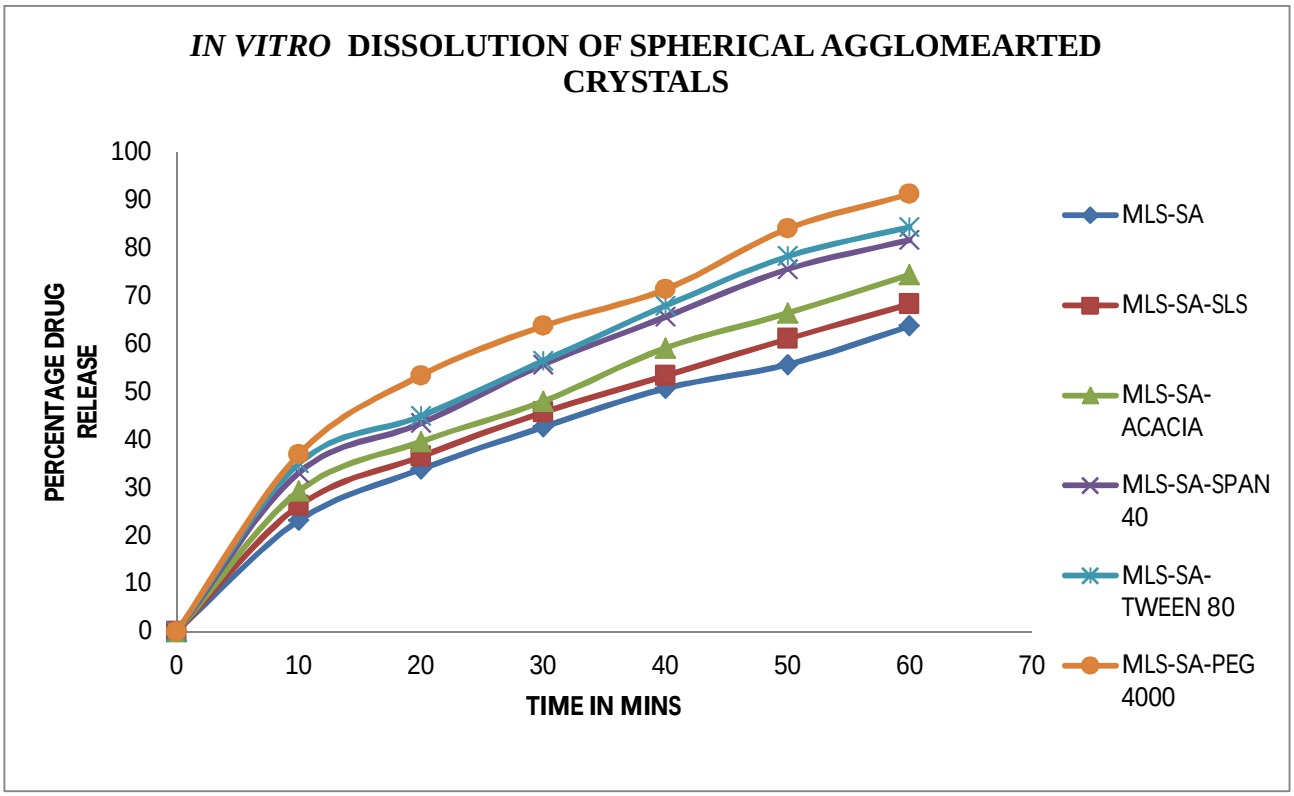

Figure 6: In Vitro Dissolution Of Spherical Agglomearted Crystals

V. CONCLUSION

In this study prepared Montelukast sodium agglomerates exhibited excellent physicochemical and micromeritic properties, solubility, dissolution rate, flowability and packability when compared with pure drug as well as the physical mixture of drug with excipients . If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed spherical agglomerates with improving the physicochemical and micromeritic properties.

VI. ACKNOWLEDGEMENTS

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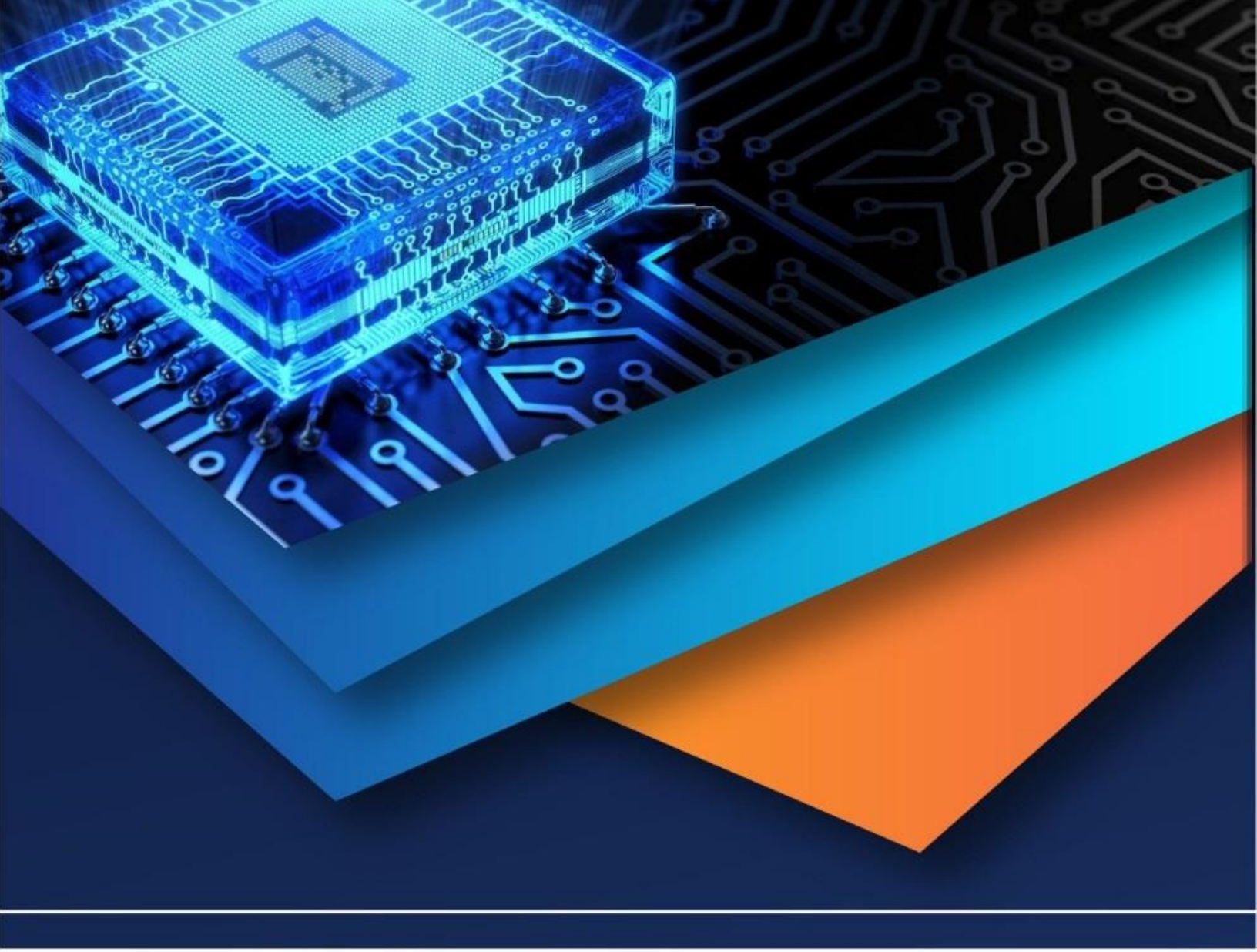

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