International Journal of Pharmaceutical Chemistry
ISSN: 2249-734X (Online)
Journal DOI: 10.7439/ijpc
CODEN: IJPCH3 (American Chemical Society)
Research Article

Pharmaceutical evaluation of effects of hydrophilicity and hydrophobicity of three commonly used diluents on tablet formulation-Part I: IR tablets

Deepak S. Khobragade*[1], Pramod Parshuramkar[2], Anusha V[1], Mrunali Potbhare[2] and Arun T. Patil[2]

[1]*Bharat Institute of Technology Hyderabad, India*
[2]*University Dept of Pharmaceutical Sci. RTM Nagpur University Nagpur, India*

Abstract

The study deals with the effects of hydrophilicity and hydrophobicity of three commonly used diluents on IR tablets of model soluble and insoluble drugs. Conventional tablets with diluents, used individually and in combinations, were prepared by direct compression, dry granulation and wet granulation. Effects of binder amount, disintegrant and its time of addition were evaluated. Tensile strength, friability, disintegration, contact angle, wettability and dissolution of tablets were assessed. Results reveal that hydrophilicity and hydrophobicity of drug and diluents markedly influence various tablet properties and should be thoroughly considered prior formulations.

Keywords: Tablets; Hydrophilicity; Hydrophobicity; Diluents; Contact angle

1. Introduction

The imperative effect produced by the drug upon administration as a solid dosage form depends on several variables such as pharmacological properties of the drug, pathological condition of the patient and physicochemical properties of the dosage form. Some of the formulation variables which are important determinants of drug action include the particle size and polymorphic form of a drug[1], excipients used in the formulation and the type of dosage form developed[2]. All of these factors, singly or combined, influence the dissolution of drug in gastrointestinal tract, its bioavailability and subsequent therapeutic effect.

As a single unit dosage form tablets have some innate advantages[3]. Along with active ingredient/s tablets contain, a number of excipients like diluents, disintegrants, binders, lubricants etc. Diluents, being principal excipients, are present in the varying amount in the range from 5-80 % of the total tablet weight and are normally thought of as inert ingredients and provide the required bulk to the tablet[4]. Diluents are also often added to tablet formulation to provide better tablet properties like improved cohesion, to allow direct compression manufacturing, to enhance flow, to adjust weight of tablet or to modify drug release.

Drug to diluents fraction can significantly regulate the biopharmaceutical, chemical and physical properties of the tablet. Various physical and chemical properties of diluents[5-6] and drugs[2] and their influence on the drug bioavailability have been evaluated in-depth[7] but very little attention has been paid towards the effect of hydrophilicity and hydrophobicity of diluents and drug on tablet properties.

This experiment was designed to assess the effect of hydrophilicity and hydrophobicity of three most extensively used diluents on tablet properties of model water soluble and insoluble drug. It is hypothesized that hydrophilicity and hydrophobicity of diluents and drugs could have palpable influence on a range of tablet properties. This effect might be distinctly increase or decrease with drug and excipient ratio. With these regards model drugs were used with constant proportion in each formulation.

* Correspondence Info
Dr. Deepak S. Khobragade
Professor,
Bharat Institute of Technology Hyderabad, India
E-mail: ksdeepak31@yahoo.co.in

2. Materials and methods

2.1 Materials

Diltiazem Hydrochloride (DTZ), freely soluble model drug, was received as a research sample from Torrent Research Centre, Ahemadabad, India. Diclofenac Sodium (DFS), insoluble model drug, was generously provided by Relief Labs Ltd, Nagpur, India. Microcrystalline Cellulose (Avicel® pH 101), Dicalcium Phosphate Dihydrate (fine powder) and Lactose Monohydrate (fine powder) were purchased from Chemfield laboratories, India, Finar Chemicals Pvt. Ltd., India and Merck Ltd., India respectively. All other ingredients were of AR grade and were used as received.

The materials were sieved through the # 60 prior use.

2.2. Experimental

2.2.1. Selection and Assessment of hydrophilicity and hydrophobicity of materials

Different diluents were selected on the basis of their solubility and swelling properties. Comparative hydrophilicity and hydrophobicity of selected diluents was assessed by contact angle study.

2.2.1a Contact angle study:[8,9]

Comparative wetting ability of materials was observed by measuring contact angle using protractor and magnifying glass technique, which having a protractor attached with the glass plate. Plain tablets of each material weighing 150 mg were prepared. Tablet was placed over the slide and kept over the glass plate attached with protractor. By placing approximately 100 µl of the water over the tablet, angle of contact between probing liquid and solid surface was measured with a thread attached to protractor and observed through magnifying glass.

2.2.1b Water absorption time[10]

Water absorption time was measured by keeping a drop of water (approximately 100 µl) over the tablet surface. Time required to absorb a drop of water by tablet was accurately noted using stopwatch and magnifying glass.

2.2.2. Preparation of tablets

Three common methods of granulation/tabletting were used for preparation of tablets of both the drugs.

2.2.2.a. Direct compression (DC)

All the materials except lubricants were mixed in a tumbling mixer for 5 minutes followed by mixing with lubricants for 2 minutes. The lubricated blend was compressed using 10 station rotary tablet machine fitted with single 8 mm plain standard concave round punch (Chamunda Pharma Machinery Pvt. Ltd. Ahemadabad) at a compression force of 3KN and rotational speed of 25 rpm to the tablets of approximately 250 mg. The formula of various batches for direct compression is given in Table No. 1.

2.2.2.b. Dry granulation (SG)

All the materials except lubricants were mixed in tumbling mixer. Slugs of 3-4 kg/cm^2 hardness were prepared using 10-station tablet machine fitted with single 13 mm flat round punch. The granules were prepared by passing the slugs through oscillating granulator (Model: UM lab type, Unimek Universal Mechanical Work Pvt. Ltd India.) fitted with 1 mm screen to get final granules of #20 and lubricated with talc and magnesium stearate for 2 minutes in tumbling mixer. After micromeritics study, lubricated blend was compressed in to tablets in similar fashion as sited in previous section.[11] The composition of tablets for different batches was kept same as that of direct compression as shown in the Table No. 1.

Table No. 1: Basic composition of Tablets

Formula (%)	DTZ	DFS	MCC	LA	DCP	Starch	Talc	Mg stearate
DTZ-M	20	-	71	-	-	6	2	1
DTZ-L	20	-	-	71	-	6	2	1
DTZ-D	20	-	-	-	71	6	2	1
DFS-M	-	20	71	-	-	6	2	1
DFS-L	-	20	-	71	-	6	2	1
DFS-D	-	20	-	-	71	6	2	1

Note: In wet granulation PVP concentration was adjusted with diluents.

2.2.2.c. Wet granulation (WG)

All the materials except disintegrant and lubricants were mixed in tumbling mixer. Granules were prepared using 5% w/w polyvinyl pyrrolidone (PVP-k30) as binder using water as granulating fluid. Dump mass was passed through # 16. Granules were dried in oven at 60°C temperature for 4 hours, passed through # 20 and after micromeritics study extragranular disintegrant and lubricants were added and compressed to tablets. The composition of tablets is shown in the Table No. 1.

2.2.3. Physical evaluation of granules[12]

The granules prepared by both the methods were passed through # 20 i.e. approximately 850 µ and analyzed for various micromeritic properties like physical appearance, angle of repose, bulk density, tapped density, % compressibility, Hausner's ratio and loss on drying (% LOD).

2.2.4. Evaluation of tablets[12]

Apart from general evaluation of friability, disintegration and hardness, tablets were further evaluated for following parameters.

2.2.4.a. Contact angle study

Contact angle of IR tablets prepared with different methods was analyzed similarly by protractor and magnifying glass technique as mentioned in section 2.2.1a.

2.2.4.b. Water absorption time

Water absorption time of IR tablets prepared with different methods was analyzed similarly as mentioned in section 2.2.1b

2.2.4.c. Radial tensile strength[13]

Radial tensile strength of tablets was calculated from the following equation

Tt = 2 Ft/ (□ Dt L)

Tt = Radial tensile strength (Mpa)

Ft = Hardness (Kg/cm^2)

Dt = Diameter of tablet (cm)

L = Thickness of tablet

2.2.4.d. Drug content

Diltiazem Hydrochloride

Twenty tablets were weighed accurately and powdered; powder equivalent to 50.0 mg of DTZ was added to 100.0 ml of distilled water to dissolve the drug. The filtrate was suitably diluted with distilled water and analyzed spectrophotometrically against blank solution for the drug content at 237 nm[14] (Shimadzu. 1601, Japan).

Diclofenac sodium

Drug content of DFS tablets was analyzed in similar fashion as that of DTZ using methanol instead of water for extracting drug and analyzed spectrophotometricaly at 276 nm[14].

2.2.4.e. *In-vitro* drug release studies

Dissolution study was performed using USP Type II apparatus, paddles rotating at 50 rpm, taking 900.0 ml of 0.1 N HCl (pH 1.2) and 6.8 pH phosphate buffer as dissolution medium for DTZ and DFS tablets respectively, maintained at $37^0C \pm 0.5^0C$. 10.0 ml of the sample was withdrawn after each 5 min for first 15 min and every 15 min thereafter and replaced with the same amount of medium. The drug release was calculated from absorbance measured spectrophotometrically at a wavelength of 237 nm and 276 nm respectively for DTZ and DFS using double beam spectrophotometer (Shimadzu. 1601, Japan).

3. Results and discussion

3.1. Assessment of hydrophilicity and hydrophobicity

Three diluents and two drugs were selected depending upon their reported solubility[14- 16]. Contact angle and water absorption time of diluents and polymers was measured to determine their comparative hydrophilicity and hydrophobicity. The contact angle, water absorption time and respective properties of selected materials are given in Table No. 2.

Table No. 2: Contact angles and properties of selected materials

Sr. No.	Material	Contact Angle	Property
1.	Lactose Monohydrate (LA)	19-21°	Water-soluble hydrophilic diluent
2.	Microcrystalline Cellulose (MCC)	37-40°	Water insoluble swellable diluent
3.	Dicalcium Phosphate Dihydrate (DCP)	43-46°	Water insoluble hydrophobic diluent
4.	Diltiazem Hydrochloride (DTZ)	-	Freely soluble drug
5.	Diclofenac Sodium (DS)	-	Insoluble drug

3.2. Physical evaluation of granules

3.2.1. *Dry Granulation*

Dry granulation as such does not have much effect of hydrophilicity or hydrophobicity of diluents or drug markedly. This reflects in less difference in density, lower Carr's index value and lower angle of repose indicating good flow properties (Table No.3). Granules after SG were having higher amount of fines (below 60#) after passing through #20 as compared to granules formed by WG in all cases.

SG was having relatively higher bulk and tapped density values than WG, which might be due to smaller particle size. Granules of hydrophobic drug and hydrophobic diluents have stronger adhesive bonding and are uniform having lower proportion of fines (Fig. 2). Granules with DCP have excellent flowability while those with MCC and lactose were having relatively lower flowability[16].

Table No. 3: Physical evaluation of granules

Drugs	Diluents	Binder solution (%)	% LOD	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (o)	% Compressibility index	Hausner ratio
Direct compression								
DTZ	**MCC**	-	5.45	0.2193	0.2522	28.69	13.04	1.150
	Lactose	-	1.81	0.2734	0.3613	27.67	24.32	1.321
	DCP	-	2.10	0.3273	0.3903	29.98	16.14	1.192
DFS	**MCC**	-	5.53	0.2061	0.2387	28.52	13.65	1.158
	Lactose	-	1.16	0.2603	0.2939	29.88	11.43	1.129
	DCP	-	1.90	0.3031	0.3497	30.96	13.32	1.153
Dry Granulation								
DTZ	**MCC**	-	5.66	0.499	0.567	42.63	11.99	1.130
	Lactose	-	1.96	0.612	0.720	42.63	15.00	1.170
	DCP	-	2.16	0.761	0.870	40.21	12.52	1.144
DFS	**MCC**	-	5.56	0.521	0.594	37.60	12.28	1.140
	Lactose	-	1.22	0.697	0.787	40.21	11.09	1.120
	DCP	-	1.97	0.837	0.893	29.75	6.27	1.075
Wet granulation								
DTZ	**MCC**	46.51	3.71	0.396	0.445	36.31	11.01	1.123
	Lactose	8.72	2.98	0.503	0.570	40.00	11.76	1.133
	DCP	19.18	2.22	0.565	0.636	35.53	11.16	1.123
DFS	**MCC**	63.95	3.56	0.513	0.590	34.04	13.05	1.150
	Lactose	23.25	2.78	0.667	0.705	36.22	5.52	1.056
	DCP	29.06	2.1	0.776	0.841	33.53	7.73	1.080

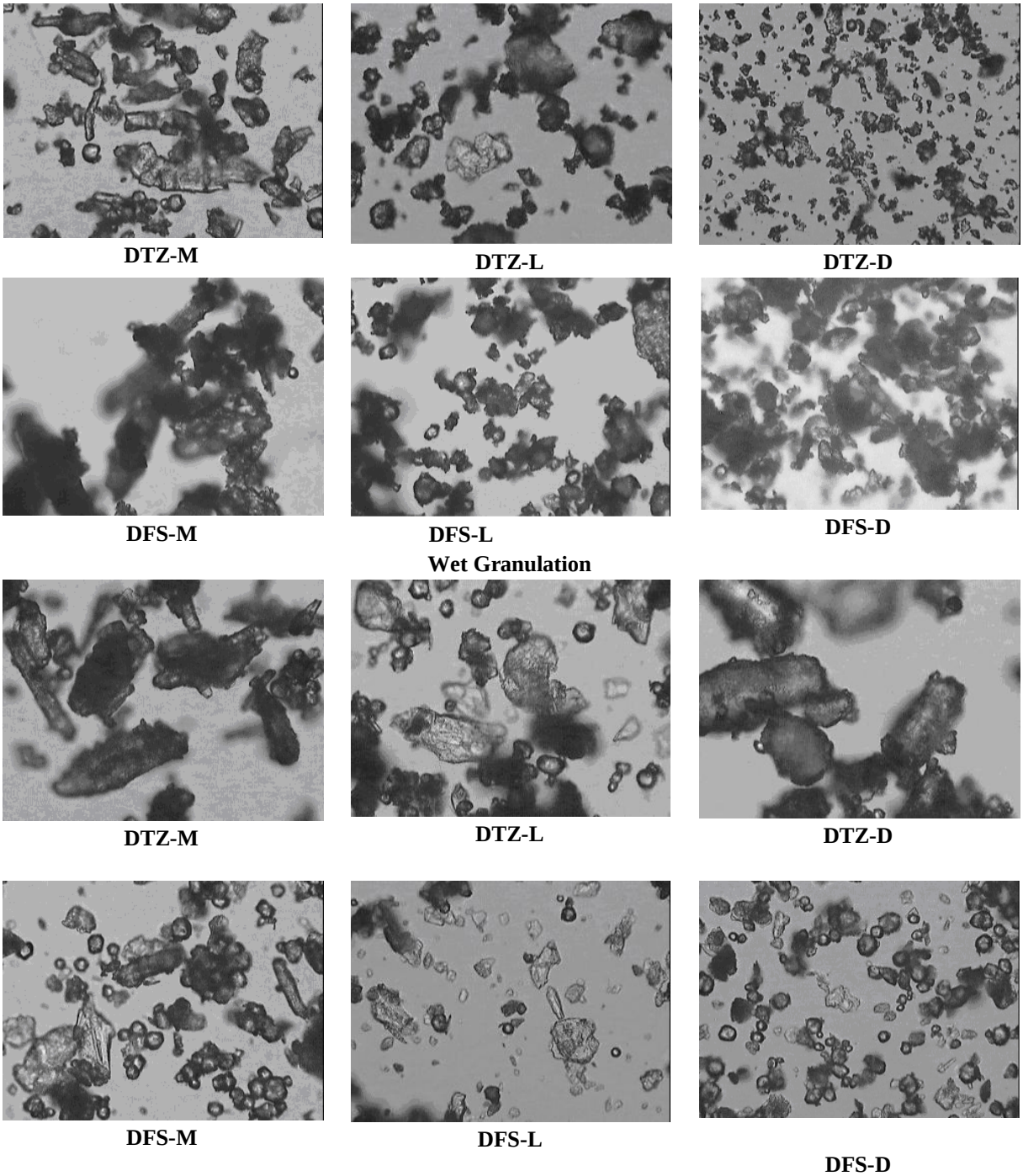
3.2.2. *Wet granulation*:

The amount of granulating fluid and type of diluent has marked effect on granulation process [17, 18]. Higher amount of granulating fluid was required for MCC based formulation. When small amount of granulating fluid was added to MCC based formulation, most of it is absorbed by MCC and does not form cohesive mass, as insufficient fluid is available on surface[19,20]. Lactose and DCP do not absorb granulating fluid and only small amount is required to form granules. In case of lactose, surface of particles, due to hydrophilicity, get dissolved in granulating fluid, which increases cohesiveness. This is not the case with DCP and cohesiveness is only imparted by binder and therefore the granules formed are brittle and greater amount of fines are generated after drying[20]. From the microphotographs in **Fig. 1** (Motic Image Plus 2) and particle size analysis Fig. 2 it can be observed that % retained on the 60 # sieve are more in MCC and lactose as compared to DCP.

The granulating fluid required for all diluents was more in case of DFS than DTZ due to increased amount of hydrophobic content in the formulation that requires relatively higher binding force to form agglomerates.

The excipients can be ranked in ascending order according to angle of repose as DCP > MCC > Lactose. Good flow properties of DCP granules might be due to higher density and more uniform granules than MCC and lactose as seen in microphotographs (Fig.1). Non uniform granules in later case might be due to swelling of MCC and solubility of lactose in granulating fluid[21].Granules with hydrophilic drugs and diluents show high angle of repose. This deterioration of the flow properties might be due to concurrent decrease in the density of the excipients, and the changes in the surface texture[22]. This might be due to crystallization of hydrophilic/soluble content on surface of granules after drying leads to surface roughening which resist the flow of granules.

Fig. 1: Microphotographs of granules formed in dry and wet granulation



3.3. Evaluation of tablets

3.3.1.*Contact angle and water penetration*

The tablets with wet granulation in all the cases show higher contact angles than tablets with direct compression and dry granulation (Table No. 4) which can be reasoned to higher amount of fines in latter cases which increase surface area remarkably and the amount of magnesium stearate used. The granules formed by wet granulation being larger in particle size and more globular shaped were more vulnerable towards effect of magnesium stearate[22]. In all the cases amount of magnesium stearate used is same which forms a relatively uniform and wholesome layering on wet granules as compared to powder material in direct compression or dry granules thus increasing surface hydrophobicity[3] and thereafter contact angle. Higher hardness and smooth surface of tablets after wet granulation, which may result in lower porosity, also aids in increasing contact angle.

Table No. 4: Physical evaluation of Tablets

Batch	Contact angle °	Water Absorption time (Sec.)	Tensile strength	Friability %	DT (min.)	D_5 (%)	% Drug Content
Direct compression							
DTZ-M	33	2.48	5.89	0.39	14.15	29.46	99.71
DTZ-L	22	3.30	5.00	1.20	1.50	89.30	98.88
DTZ-D	42	4.33	5.96	1.41	0.40	91.21	100.1
DFS-M	40	5.44	7.02	0.53	2.15	13.00	99.38
DFS-L	35	5.55	4.11	13.50	2.54	53.56	98.77
DFS-D	52	11.48	5.99	0.83	0.42	57.29	99.73
Dry granulation							
DTZ-M	31	1.63	5.88	0.41	0.20	97.62	99.37
DTZ-L	26	4.48	4.60	2.58	1.55	96.05	98.97
DTZ-D	48	2.21	6.16	30.60	0.30	73.28	99.18
DFS-M	37	3.09	5.22	0.20	0.40	80.59	99.92
DFS-L	36	6.79	4.11	0.31	0.58	84.00	99.74
DFS-D	53	16.45	5.90	0.43	3.20	54.32	100.03
Wet granulation							
DTZ-M	57	85.85	6.57	0.09	47.30	11.86	98.58
DTZ-L	42	20.54	4.61	0.13	5.0	52.65	99.47
DTZ-D	56	23.32	6.44	0.13	6.05	36.67	98.95
DFS-M	69	39.87	5.02	0.13	20.20	5.62	99.66
DFS-L	51	22.79	5.36	0.22	9.45	17.33	98.22
DFS-D	66	680.13	7.17	0.37	15.20	6.86	98.73

Water absorption by tablets depends on the porosity of tablet and surface wetting ability influenced by the hydrophilic and hydrophobic nature of materials used. In more porous tablets wetting can be decreased by the hydrophobicity imparted by used materials.

Water penetration rate in the tablets by wet granulation is less than dry granulation followed by direct compression with respective excipients and drugs[23]. Although MCC is water insoluble tablets have rapid water penetration rate as compared to LA in case of DC and SG tablets due to swelling property of MCC. Tablets containing DCP and hydrophobic drug show slow water penetration because of decreased tablet wetting ability due to imparted hydrophobicity.

3.3.2. *Tensile strength and friability*

The compression force was kept constant i.e. 3KN for all formulations. At the same compression force MCC produced tablets with higher hardness followed by lactose and DCP. MCC, having excellent tensile strength and minimum % friability undergoes significant plastic deformation during compression bringing an extremely large surface area in to close contact and facilitating hydrogen bond formation between the plastically deformed, adjacent particles[18,20]. Lactose produced soft compacts due to fragmentation that creates a large number of small particles thus the number of contact points that support the applied load is larger and the stress on each contact point is relatively small with the formation of weak bonds in tablet[18,24]. Lactose shows low % friability with hydrophilic drug as compared to hydrophobic drug, might be due to increased bond strength between hydrophilic drug and hydrophilic excipients. Tablets with DCP have more % friability due to the brittle nature of DCP[24,25]. It undergoes considerable fragmentation during compression[23,26]. Fracture creates a large number of interparticulate contact points, which imply that a comparatively feeble type of bonding is involved, thus the tablet

shows more % friability. DCP having acceptable % friability with hydrophobic drug, this is due to the drug-diluent hydrophobic interaction overcoming the fragmentation.

3.3.3. *Disintegration time (DT)*

DC tablets containing LA have less DT due to water solubility of LA. Tablets with hydrophobic drug have longer DT as compared to tablets with hydrophilic drug. DC tablets containing DCP shows fast tablet disintegration as compare to MCC and LA due to less compactness of tablets. DC tablets of MCC with hydrophilic drug shows relatively higher DT as compared to LA and DCP due to the binding and swelling properties of MCC resisting the breaking of tablet, and allowing only diffusion of medium and delaying tablet breaking[27]. MCC with hydrophobic drug requires less time for disintegration because of increased interparticulate distance due to presence of water insoluble drug particles which strengthen the hydrodynamic force created by the swelling of MCC with scarce space available. This propels neighboring particles more forcefully to disintegrate the tablet rapidly.

In dry granulation the relatively higher porosity of tablet helps rapid tablet disintegration[26]. In tablets with hydrophobic drug disintegration rate is also assisted due to additional effect of surface erosion of drug[28].

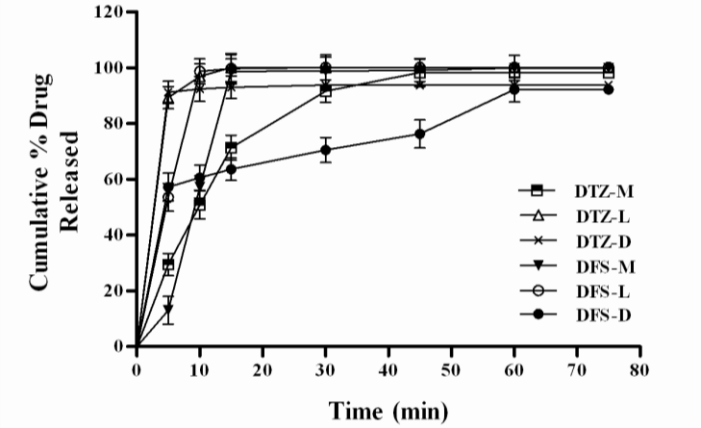
In case of wet granulation DT is further increased due to additive biding properties of MCC with PVP accomplice to its inherent binding and swelling capacity. This effect is even seen with hydrophobic drug. WG tablets containing LA and DCP have low DT with hydrophilic drug. The higher solubility of lactose and drug easily break the tablet in first while pores formed by freely soluble drug create rapid erosion of tablet in later case. But it is comparatively more in case of DCP tablets with hydrophobic drug, in which both the drug and diluents are hydrophobic, resist entry of water, thus increasing DT.

3.4. *In-vitro* drug release study

3.4.1. *Tablets prepared by DC*

Formulation DTZ-M shows slow rate of release as compared to formulation with lactose and DCP (F_2 21 and 22 respectively). Long disintegration time might be responsible for slow release from these tablets (**Fig. 2**). Dissolution of DTZ may accommodate the swelling MCC and starch particles, permitting little or no disintegrating force development. Water soluble DTZ competes with MCC and starch for a limited amount of available water inside the tablet which is required for swelling and disintegration[29]. Formulation DTZ-L shows short disintegration time as lactose acts as passive disintegrant[30,31] by dissolution and shows burst release. In case of DTZ-D freely soluble drug forms pores in hydrophobic adjoining allowing hasty entry of medium which leads to fast erosion of matrix giving immediate release. Despite of different release mechanism, DTZ-D and DTZ-L shows similar release profile (F_2 62). The different hydration kinetics of DTZ and DCP producing greater disruptive shear forces and shorter disintegration times might be reasoned for this.

Fig. 2: *In-vitro* drug release from tablets with direct compression



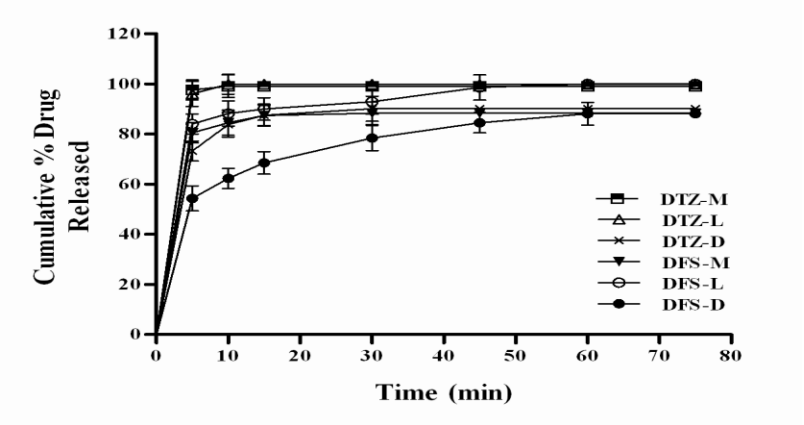
DFS-M shows slower initial release due to swelling of MCC which decreases rate of penetration and subsequent solubelization of drug, as soon as tablet disintegrates complete release was observed in 15 minutes. DFS-L shows faster release as compared to DCP and MCC and shows complete release in 10 minutes. Surprisingly DFS-D though having lowest disintegration time and highest initial drug release, total time required for complete drug release was prolonged above 75 minutes[31]. Due to difference in dissolution calculations of the similarity factor were irrelevant.

Formulation DFS-M shows faster drug release as compared to DTZ-M due to decreased disintegration time as explained in previous section. DFS-L gives release in similar manner as that for DTZ after initial relatively slower release caused by increased initial wetting time[32-36]. Formulation DFS-D shows comparatively slow release due to hydrophobic nature of drug and excipients prolonging wetting of tablets by dissolution media.

3.4.2. *Tablets prepared by SG*

Formulations by SG show faster release as compared to DC and WG (**Fig. 3**). Water soluble and water insoluble drugs both show similar release pattern but only initial release differs with different excipients [37]. DCP shows slow initial release than MCC and lactose this might be due to decreased wettability imparted by hydrophobicity. The release profile of DFS-M and DFS-L formulation was similar (F_2 62) than release profile DFS-D ($F_2$37).

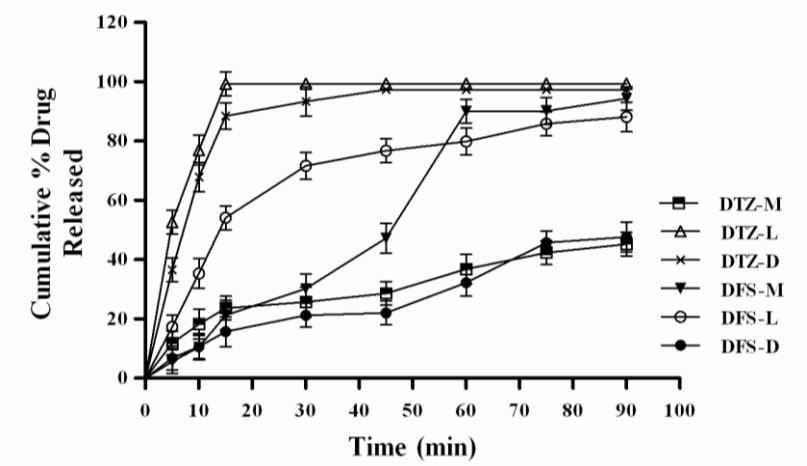
Fig. 3: *In-vitro* drug release from tablets with dry granulation



3.4.3. *Tablets prepared by WG*

Increased particle size of granules and reduced surface area allows better covering of granules by magnesium stearate which makes the surface hydrophobic (as reflected with increased contact angle) and water penetrates slowly[38]. Formulation DTZ-M shows very slow release due to additive binding of MCC with PVP which increases DT and the release occurs by diffusion, solublizing and releasing drug slowly (**Fig. 4**). Formulation DTZ-L shows fast release due to hydrophilic nature of lactose and drug, undergoing early disintegration with instant drug release. Formulation DTZ-D shows intermediate rate of release as it forms hard tablets, which disintegrate quite slowly than lactose (F_2 54) and faster than MCC tablets (F_2 12). Here too drug releases by erosion, DTZ facilitating medium penetration and bringing disintegration.

Fig. 4: *In-vitro* drug release from tablets with wet granulation



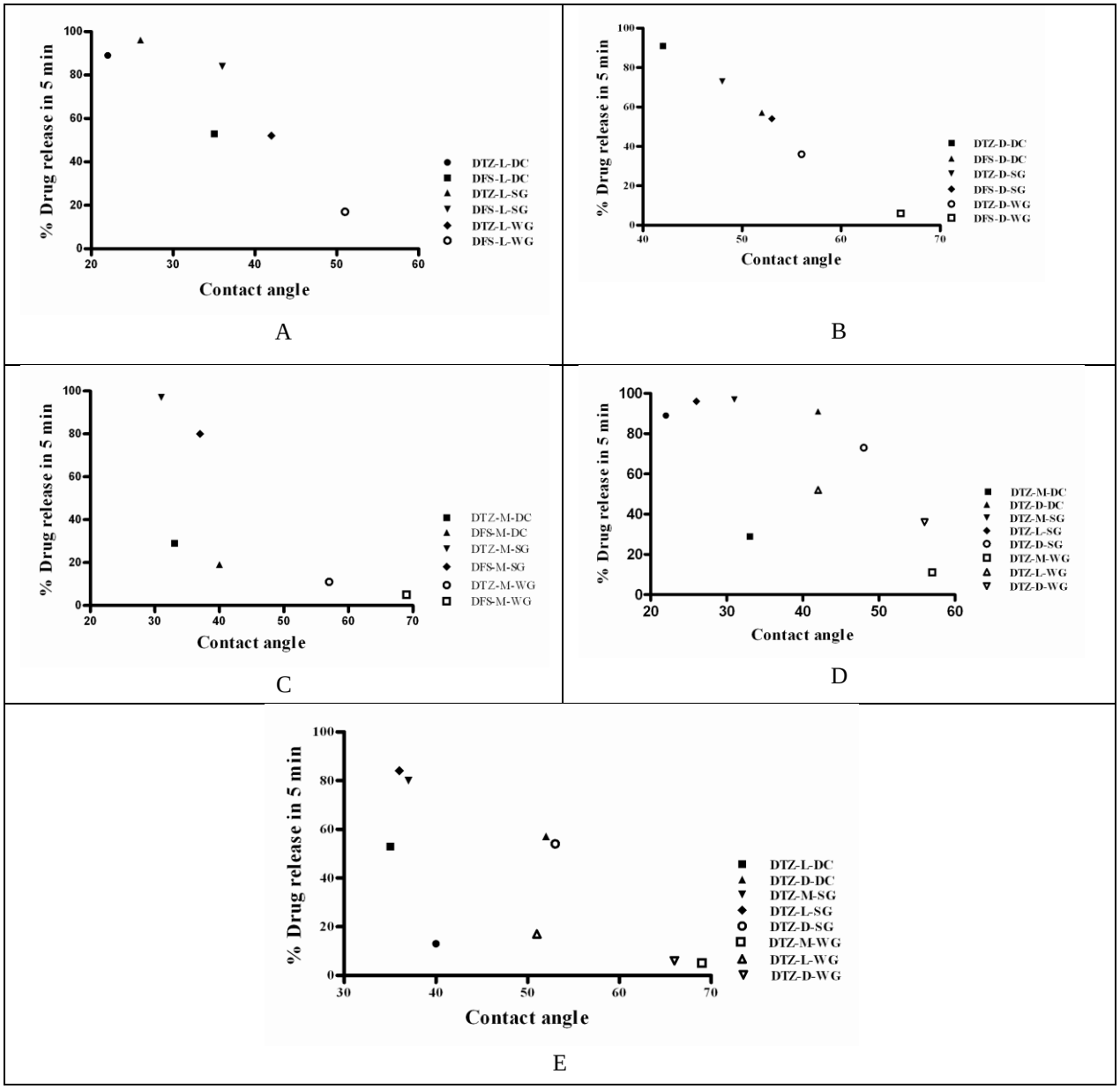
Formulation DFS-M although shows slow initial release still the complete dissolution occurs in 60 minutes, governed by the delayed disintegration[39-41]. DFS-L shows faster release than both other diluents. DFS-D shows slowest release and less than 50% drug was released in 90 minutes this might be due to delayed disintegration of tablet in to granules which required additional time to break in to fine particles and was rate limiting step for dissolution. All dissolution profiles were dissimilar and shows F_2 value below 50.

3.4.4. *Effect of wettability/ contact angle on drug release*

The Lactose and DCP based formulation shows apparent correlation between drug release and contact angle[42-44]. As contact angle increases drug release decreases but in case of MCC based formulation there is no explicit correlation between contact angle and drug release (Fig. 5 A, B and C). This might be due to other factors like tablet porosity, method of granulation and drug solubility playing a more decisive role in drug release[45].

DTZ tablets shows decrease in drug release as contact angle increases above 50, below that there is no significant effect on drug release except with MCC based formulation (Fig. 5 D). In case of DFS tablet the correlation is more complex (Fig. 5 E).

Fig. 5 Effect of contact angle on drug release in 5 min (D_5)



4. Conclusion

Inference can be drawn that hydrophilicity and hydrophobicity are the indispensable properties with regard to formulation of solid dosage form as they evidently affect the overall processing and product parameters like degree of cohesiveness, granulation, flow properties, compression behavior, physical strength, disintegration and dissolution rate of formulations. The results of the present study confirm that the, contact angle and water penetration of tablets are governed by hydrophilicity of diluents and drug and affects initial drug release. Wet

granulation was found to be most prone process for effects of diluents. Increased hydrophilic content decreases amount of binder solution required for granulation. Despite of having hydrophilic nature MCC shows slower drug release both in wet granulation and direct compression. In direct compression insoluble hydrophilic diluent MCC increases disintegration of DTZ. DFS shows improved flow properties with hydrophobic diluent like DCP than MCC and LA. Nonetheless having short disintegration time DCP shows slow release in case of water insoluble drug DFS. In dry granulation drug release is not affected by type of diluents.

References

[1] Robinson JR. Influence of drug properties and route of drug administration on the design of sustained and controlled release systems. In: *Controlled drug delivery: Fundamentals and applications*. 2nd Ed. New York; Marcel Dekker Inc.; 1978:3-4.

[2] Lieberman H, Rieger M, Banker G. Excipients and formulation. In: *Pharmaceutical dosage forms*. Vol. 2, New York; Marcel Dekker, Inc.; 1987:151-213.

[3] Bendgude Namdeo Tukaram, Iyer Vidaya Rajagopala, Poddar Sushil Kumar Shartchandra. The Effects of Lactose, Microcrystalline Cellulose and Dicalcium Phosphate on Swelling and Erosion of Compressed HPMC Matrix Tablets: Texture Analyzer. *Iranian J Pharm Res.* 2010; 9 (4): 349-358.

[4] Bogda MJ. Tablet Compression: Machine Theory, Design, and Process Troubleshooting. In: Swarbrick J eds. *Encyclopedia of Pharmaceutical Technology*. Vol. 6. 3rd Ed., New York, Informa Healthcare USA, Inc.; 2007:3611.

[5] Danish FQ, Parrott EL. Flow rate of solid particulate pharmaceuticals. *J Pharm Sci*. 1971; 60:548-554.

[6] Sangekar SA, Sarli M, Seth PR. Effect of moisture on physical characteristics of tablets prepared from direct compression excipients. *J Pharm Sci*. 1972; 61:939-944.

[7] Lerk CF, Bolhuis GK, Deboer AH. Pharmaceutical dosage forms-tablets. *Pharm Weekblad.* 1974; 109:945-955.

[8] York P. Solid state properties of powders in the formulation and processing of solid dosage forms. *Int J Pharm.* 1983; 14:1-28.

[9] Zografi G, Tam SS. Wettability of pharmaceutical solids: Estimates of solid surface polarity, *J Pharm Sci.* 1976; 65:1145-1149.

[10] Nande VS, Barabde UV, Morkhade DM, Patil AT, Joshi SB. Synthesis and characterization of PEGylated derivatives of rosin for sustained drug delivery. *React Funct Polym.* 2006; 66:1373-1383.

[11] Buchi N. Nalluri, S. Vidyasagar and K. M. Maheswari. Effect of Excipients on Oxcarbazepine Release from Modified Release Matrix Tablets. *J Applied Pharm Sci.* 2012; 02 (08): 150-158.

[12] Levina M, Rajabi- Siahboomi AR. The influence of excipients on drug release from HPMC matrices. *J Pharm Sci*. 2004; 93 (11):2746-2754.

[13] Martin A, Swarbric J, Cammarata A. Micromeritics. In: *Physical pharmacy*. 3rd Ed. Bombay, K. M. Varghese Company; 1991:515–519.

[14] Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman H, Kanig J,eds. *The theory and practice of industrial pharmacy*. 3rd Ed. Bombay, K. M. Varghese Company; 1987:297–345.

[15] Zhang YE, Schwartz JB. Effect of diluents on tablet integrity and controlled drug release. *Drug Dev Ind Pharm.* 2000; 26(7):761-765.

[16] Ashok Kumar P.1 and Damodar Kumar S. Effect of hydrophilic and hydrophobic polymers and fillers on controlled release matrix tablets of acyclovir. *Der Pharmacia Sinica*, 2013; 4(3): 143-150.

[17] *United States Pharmacopeia and National Formulary* [CD-ROM] USP 30-NF 25; 2007: I st supplement.

[18] Rowe RC, Shesky PJ, Weller PJ. *Handbook of pharmaceutical excipients.* 4th Ed. Pharmaceutical Press and American Pharmaceutical Association of Great Britain, 2003.

[19] Lee YSL, Poynter R, Podczeck F, Newton JM. Development of dual approach to assess powder flow from avalanching behavior. *AAPS Pharmscitech*. 2000; 1(3):21.

[20] Pranjali Gawali, Anand Gupta, Sayali Kachare, Sanjay Kshirsagar. Formulation and Evaluation of Matrix-based Sustained Release Tablets of Quetiapine fumarate and the Influence of Excipients on Drug Release. *J Chem Pharm Res* 2012; 4(6):3073-3081.

[21] Soh JLP, Liew CV, Heng PWS. Torque rheological parameters to predict pellet quality in extrusion–spheronization. *Int J Pharm.* 2006; 315:99–109.

[22] Michel de Bastos. O, Rossana Friedrich. B, Ruy Beck. C.R. Effects of Filler-Binders and Lubricants on Physicochemical Properties of Tablets Obtained by Direct Compression: A 22 Factorial Design. *Lat. Am. J. Pharm.* 2008; 27(4): 578-83.

[23] Tsai T, Wu JS, Sheu MT. Modification of physical characteristics of microcrystalline cellulose by codrying with beta cyclodextrins. *J Pharm Sci*. 1998; 87(1):117-122.

[24] Lakshmi Prasanna J, Deepthi B, Rama Raon. Influence of Diluents on Diclofenac Sodium Release from Gum Kondagogu Based Matrix Tablets. *Int J Pharm Res and Rev*.2012; 1(4): 12-20.
[25] Heng PWS, Wan LSC, Ling BL. Assessment of powder cohesiveness in spheronization studies. *Int. J. Pharm.* 1995;116:119-123
[26] Cole ET, Rees JE, Hersey JA. Relations between compaction data for some crystalline pharmaceutical materials. *Pharm Acta Helv*. 1975; 50(1-2):28-32.
[27] Cal S, Iglesias G, Souto C, Concheiro A, Gdmez-Amoza JL, Martinez-Pacheco R. Effects of hydration on the properties of a roller-dried fl-lactose for direct compression. *Int J Pharm.* 1996; 129:253-261.
[28] Wu J, Ho H, Sheu M. Influence of wet granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose with b-cyclodextrin. *Eu J Pharm Biopharm.* 2001; 51:63-69.
[29] Maarschalk K, Bolhuis GK. Improving properties of materials for direct compression. *Pharm Tech Europe*. 1998; 10(9):30-35.
[30] Jivraj M, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. *PSTT*. 2000; 3(2):58-63.
[31] Roberts RJ, Rowe RC. The Young's modulus of pharmaceutical materials. *Int J Pharm*. 1987; 37:15-18.
[32] Horisawa E, Danjo K, Sunada H. Influence of granulating method on physical and mechanical properties, compression behavior, and compactibility of lactose and microcrystalline cellulose granules. *Drug Dev Ind Pharm.* 2000; 26(6):583-593.
[33] Varma MVS. Kaushal AM, Garg A, Garg S. Factors affecting mechanism and kinetics of drug release from matrix based oral controlled drug delivery systems. *Am J Drug Deliv.* 2004; 2(1):43-57.
[34] Murakami H, Yoneyama T, Nakajima K, Kobayashi M. Correlation between loose density and compactibility of granules prepared by various granulation methods. *Int J Pharm.* 2001; 216:159–164.
[35] Lopez-Solis J, Villafuerte-Robles L. Effect of disintegrants with different hygroscopicity on dissolution of Norfloxacin: Pharmatose DCL 11 tablets. *Int J Pharm.* 2001; 216:127–135.
[36] Van Kamp HV, Bolhuis GK, Kussendrager KD, Lerk CF. Studies on tableting properties of lactose. IV. Dissolution and disintegration properties of different types of crystalline lactose. *Int J Pharm.* 1986; 28:229–238.
[37] Johnson JR, Wang LH, Gordon MS, Chowhan ZT. Effect of formulation solubility and hygroscopicity on disintegrant efficiency in tablets prepared by wet granulation, in terms of dissolution. *J Pharm Sci.* 1991; 80:469-471.
[38] Shalaka dhat, Sanjivani aphale, Uddhav bagul, Amol Tagalpallewar, Swapnila vanshiv, Nisarg shah. Effect of two different diluents on release profile of Aceclofenac fromSustained release matrix tablets using gum Damar as release retardant. *Int J Pharm Pharm Sci.* 2011; 3(4): 307-313.
[39] O. N. C. Umeh. Effect of hydrophilic diluents on the release profile of griseofulvin from tablet formulations. *Indian J Pharm Sci.*2013; 75(6): 726-729.
[40] Michael U. Uhumwangho, Roland S. Okor. A Comparative study of the dissolution characteristics of capsule and tablet dosage forms of melt granulations of Paracetamol - diluent effects. *Acta Poloniae Pharmaceutica - Drug Research*. 2007; 64(1): 73-79.
[41] Zhang. YE, Schwartz.JB. Effect of diluents on tablet integrity and controlled drug release. Drug Dev Ind Pharm. 2000; 26(7): 761-765.
[42] Lakshmi Prasanna J, Deepthi B, Rama Raon. Influence of Diluents on Diclofenac Sodium Release from Gum Kondagogu Based Matrix Tablets. *Int J Pharma Res & Rev*. 2012; 1(4):12-20.
[43] Ancuta Catalina Fita, Dumitru Lupuleasa, Teodora Dalila Balaci, Oana Karampelas, Emma Budura. The influence of some diluents on the release of Metoprolol tartrate from prolonged release matrix tablets. *Practica Farmaceutică*. 2011; 4(3):192-194.
[44] Panagopoulou. A, Georgarakis. M. Effect of compression and diluent on drug release from matrix tablets. a statistical analysis. *Drug dev Ind Pharm.*1990; 16(4): 637-649.
[45] Hani, Umme Shivakumar H.G, Srivastava, Atul, Rashmi N.G, Shinde.G, Chetan. Influence of Diluents on Release Properties of Curcumin-Hydroxy Propyl β Cyclodextrin Bioadhesive Vaginal Tablet. *Current Drug Therapy*. 2014; 9(2): 75-82.