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Research Article

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

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Abstract

Effects of hydrophilicity and hydrophobicity of three commonly used diluents on characteristics and functioning of sustained release tablets were assessed. Tablets of model soluble and insoluble drugs were formulated with HPMC and ethyl cellulose. Hardness, friability, disintegration, contact angle, wettability and dissolution of tablets were studied. These sustained release formulations were noticeably affected by hydrophilicity and hydrophobicity of drug and diluents and should be meticulously given a thought.
Keywords: SR Tablets; Hydrophilicity; Hydrophobicity; Diluents; HPMC; Ethyl Cellulose

1. Introduction

Swellable and erodible systems prepared by incorporating drugs in polymeric matrices have received considerable attention for sustained release formulations. Hydroxyl propyl methylcellulose (HPMC) and ethyl cellulose are frequently used as hydrophilic polymer and hydrophobic polymer respectively due to their non-toxic nature, ease of manufacturing and other advantages[1,2]. Several important formulation variables such as polymer concentration, polymer viscosity grade, dosage size and manufacturing process have been evaluated[3-5]. Among these variables, concentration and viscosity grade mostly affect drug release profiles both kinetically and mechanistically[6]. Other important factors in modulating drug release from monolithic matrix tablets include the type and quantity of drug and excipients. Insoluble diluent dicalcium phosphate dihydrate in matrix tablets containing insoluble drug and HPMC K4M decreased the rate and extent of drug release compared with the same matrix containing soluble diluent lactose[7]. No attention was paid to the role of excipients on actual release mechanism(s). Various physical and chemical properties of diluents[8-9] and drugs and their influence on the drug bioavailability have been evaluated[10] but very little attention has been paid towards the effect of hydrophilicity and hydrophobicity of diluents on tablet properties and drug release. The purpose of this study was to investigate in detail the influence of hydrophilicity and hydrophobicity of three common diluents on the kinetics of drug release from matrix system containing water-soluble and insoluble drug[10].

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, HPMC K4M was received as gift sample from Colorcon India Ltd. Ethyl Cellulose (20 cps), Microcrystalline Cellulose (Avicel® pH 101), Dicalcium Phosphate Dihydrate (fine powder) and Lactose Monohydrate (fine powder) were purchased from Loba Chemicals Ltd. India, Chemfield laboratories, India,

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Finar Chemicals Pvt. Ltd., India and Merck Ltd., India respectively. All other ingredients were of AR grade and were used as received. The contact angle and respective properties of individual excipient are given in Table no.1.

Table No. 1: Contact angle 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.	HPMC (K4M)	63-65°	Swellable hydrophilic polymer
5.	Ethyl Cellulose (EC)	83-85°	Water insoluble hydrophobic polymer
6.	Diltiazem Hydrochloride (DTZ)	-	Freely soluble drug
7.	Diclofenac Sodium (DS)	-	Insoluble drug

The materials were sieved through the # 60 prior use.

2.2. Experimental

2.2.1. Preparation of tablets

The sustained release tablets for DTZ and DFS were prepared by wet granulation. Tablets of HPMC were prepared by wet granulation using isopropanol : water (4:1) mixture as granulating fluid as per the formulas given in Table No. 2. All the materials except lubricants were sufficiently wetted with granulating fluid, dried at 60ºC and passed through 20#. For preparing EC matrix tablets all the materials as per formula (Table No. 3) except lubricants were triturated with the EC solution in ethanol, dried and passed through # 20 to form granules. The lubricated blends were 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. Sustained release tablets were also prepared using combination of two diluents for both the drugs and polymers to evaluate combined effect of diluents on release profile.

Table No. 2: Composition of tablets with HPMC

Formula (%)	DTZ	DFS	MCC	LA	DCP	HPMC	Talc	Mg St
DTZ-M	20	-	57	-	-	20	2	1
DTZ-L	20	-	-	57	-	20	2	1
DTZ-D	20	-	-	-	57	20	2	1
DFS-M	-	20	57	-	-	20	2	1
DFS-L	-	20	-	57	-	20	2	1
DFS-D	-	20	-	-	57	20	2	1

Table No. 3: Composition of tablets with EC

Formula (%)	DTZ	DS	MCC	LA	DCP	EC	Talc	Mg St
DTZ-M	20	-	72	-	-	5	2	1
DTZ-L	20	-	-	72	-	5	2	1
DTZ-D	20	-	-	-	72	5	2	1
DFS-M	-	20	72	-	-	5	2	1
DFS-L	-	20	-	72	-	5	2	1
DFS-D	-	20	-	-	72	5	2	1

2.2.3. Evaluation of granules[11]

The granules prepared 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 ratio and free drug content.

2.2.4. Evaluation of SR tablets

The tablets were evaluated before drug release study for percent friability, drug content, contact angle and water absorption time. Apart from general evaluation of friability, disintegration and hardness, tablets were further evaluated for Contact angle[12,13] and Water absorption time[2].

2.2.4.a. 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 6.8 pH phosphate buffer and sonicated for 10 min (Sonicator 3.5 L100, PCI Instruments India.). Filtrate was suitably diluted and analyzed spectrophotometrically against blank solution for the drug content at 237 nm (Shimadzu. 1601, Japan).

Diclofenac sodium: Drug content of DFS tablets was analyzed in similar means as that of DTZ except that the solution was sonicated for 20 minutes and analyzed spectrophotometrically at 276 nm.

2.2.4.b. *In-vitro* drug release study

In-vitro drug release study of both the drugs was performed using USP Type II apparatus rotated at 50 rpm employing 900 ml of 0.1 N HCl, for first two hours, and pH 6.8-phosphate buffer thereafter as dissolution medium. 10.0 ml sample was withdrawn at every hour interval and reinstate with same quantity of fresh 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).

2.2.4.b. Scanning Electron Microscopy (SEM)

After dissolution study, matrix topography of the SR tablets was examined by scanning electron microscope (JEOL JSM-6380A Analytical SEM). Sputtering of the dried tablets with palladium using JEOL JFC-1600 Auto Fine Coater was carried out prior scanning by electron microscope.

3. Results and discussion

3.1. Evaluation of granules

Granulation of DTZ with HPMC required to be carried out with slow addition granulating fluid with mixing as small excess produces localized over wetting with plastic lump formation which was impractical for further processing into granules or caused loss of material due to sticking .Granules of DCP show good flow properties with HPMC than MCC and lactose. DCP granules show comparatively good flow properties than MCC and lactose. DFS granulation was quite easier and required slightly more quantity of granulating fluid. The DFS granules were having higher amount of fines but were more uniform than DTZ granules. The bulk density ad tapped density of DFS granules was higher (Table No.4). EC granules with all diluents were fragile and produced more amounts of fines than that of HPMC granules. No significant difference in flow properties observed between granules of different diluents.

Table No. 4: Physical evaluation of granules

Drugs	Diluents	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (o)	Compressibility index %	Hausner ratio	Free drug content %
With HPMC							
DTZ	MCC	0.4102	0.4745	36.58	13.5511	1.1567	33
	LA	0.4501	0.5160	39.40	12.7713	1.1464	38
	DCP	0.6566	0.7373	34.51	10.9453	1.1229	36
	MCC+LA	0.4414	0.4938	37.01	10.6115	1.1187	35
	MCC+ DCP	0.6132	0.7234	35.66	15.2336	1.1797	33
	LA+DCP	0.6446	0.7420	33.14	13.1266	1.1511	39
DFS	MCC	0.4517	0.5190	34.67	12.9672	1.1489	2.6
	LA	0.5264	0.6316	37.00	16.6561	1.1998	5.8
	DCP	0.7378	0.8272	31.3	10.8075	1.1211	1.2
	MCC+LA	0.4615	0.5107	37.96	9.63383	1.1066	3.4
	MCC+ DCP	0.6103	0.6855	36.65	10.9700	1.1232	2.1
	LA+DCP	0.7142	0.8015	32.42	10.8920	1.1222	3.9
With EC							
DTZ	MCC	0.4335	0.578	33.34	25.0000	1.3333	18
	LA	0.5647	0.9071	37.85	37.7466	1.6063	22
	DCP	0.6479	0.9036	33.11	28.2979	1.3946	15
	MCC+LA	0.5016	0.6945	32.55	27.7753	1.3845	23
	MCC+ DCP	0.5823	0.7765	32.01	25.0096	1.3335	17
	LA+DCP	0.6353	0.9530	33.46	33.3368	1.5000	19
DFS	MCC	0.4003	0.6250	34.90	35.9520	1.5613	0.4
	LA	0.6250	0.8333	38.29	24.9970	1.3332	0.8
	DCP	0.7030	0.7697	32.94	8.6657	1.0948	0.2
	MCC+LA	0.4545	0.6610	34.53	31.2405	1.4543	0.4
	MCC+ DCP	0.5882	0.6817	33.51	13.7157	1.1589	0.5
	LA+DCP	0.6666	0.9090	36.46	26.6666	1.3636	0.5

HPMC shows higher free drug content as compared to EC in all the formulations. EC granulation was carried out using EC in solution form which formed uniform distribution with better entrapment within the granules rather HPMC was used in powder form due to which higher extent of free drug was observed. Imparted hydrophobicity due to EC also increases contact angle and water absorption time and therefore drug take more time to be dissolved. One reason might be the higher solubility of DTZ resulting in faster dissolution in eluting medium while DFS being poorly soluble shows low free drug content. Higher solubility of DTZ outweighed the different diluents properties and no significant differences were observed in free drug contents, in contrast in case of DFS DCP shows lower free drug content than MCC and Lactose thus indicating that the diluents have a say in the solubilization and subsequent values of free drug content.

3.6. Evaluation of SR tablets

After formulation, sustained release tablets were evaluated for physical parameters (Table No. 5). All formulation batches were having hardness in the range of 4.8 – 5.5 kg/cm^2 with good enough friability values (< 0.5%) and drug content. It was observed that formulations with EC demonstrated higher contact angle and water absorption time as compared to formulations with HPMC.

Table No.5: Evaluation of Tablets

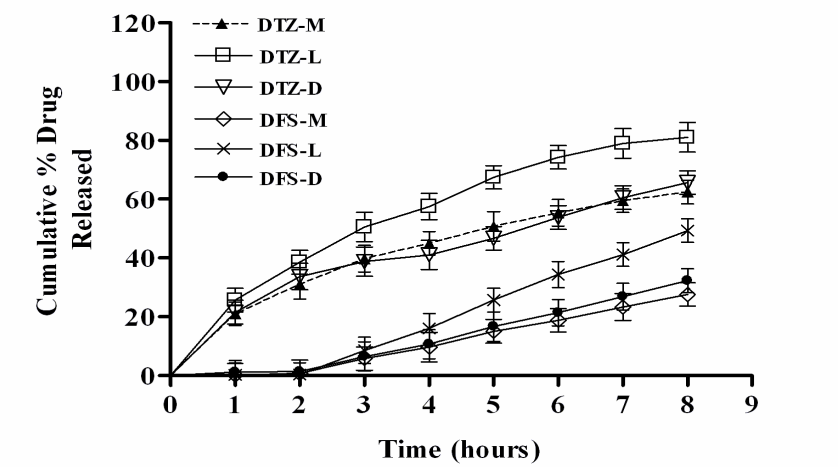
Batch	**Friability** %	**Drug content** %	**Contact angle** (o)	**Water absorption time** (sec)
HPMC Tablets				
DTZ-M	0.122	99.36	46.0	43.77
DTZ-L	0.217	98.98	37.0	31.71
DTZ-D	0.321	100.2	49.0	4.3
DFS-M	0.210	98.39	51.0	119
DFS-L	0.325	99.99	41.0	300
DFS-D	0.218	99.32	56.0	16.26
EC Tablets				
DTZ-M	0.112	97.64	57.0	43.21
DTZ-L	0.190	97.94	53.0	61
DTZ-D	0.169	96.99	61.0	18
DFS-M	0.211	99.02	67.0	225
DFS-L	0.202	99.37	51.0	262
DFS-D	0.163	99.00	73.0	22

Formulations with MCC exhibit less absorption time as compared to LA because of swelling nature. LA initially takes more time showing slow rate of absorption followed by swift absorption. Formulations with DCP illustrate higher contact angles than other formulations but require less water absorption time, might be because of surface characteristics. Formulations with sparingly soluble drug have elevated contact angle values and show additional absorption time as compared to freely soluble drug with particular diluent and polymer.

3.6.1. *In-vitro* drug release from hydrophilic polymer matrix

In-vitro drug release profile of both the drugs from hydrophilic HPMC matrix is shown in **Fig. 1.** Hydrophilic matrix on exposure to aqueous medium starts hydrating to form gel layer and start dissolving or eroding. The drug mainly release by diffusion through gel layer, when water reaches the towards the core of tablet, the diameter of gel layer increases and the concentration of drug falls and release rate of drug begins to reduce. An initial fast release of hydrophilic drug occurs due to surface leaching and time taken by high viscosity grade polymer to form gel layer due to delayed hydration[14]. The increase in thickness of the barrier layer with time increase diffusion path reduce rate of release. In case of tablets with insoluble drug, though the polymer is same and forms the gel layer with similar rate as with soluble drug, drug being less soluble the rate of diffusion is very slow and sparingly soluble drug dispersed in hydrophilic matrix is primarily released by erosion[15].

Fig. 1: *In-vitro* drug release from tablets with HPMC matrix



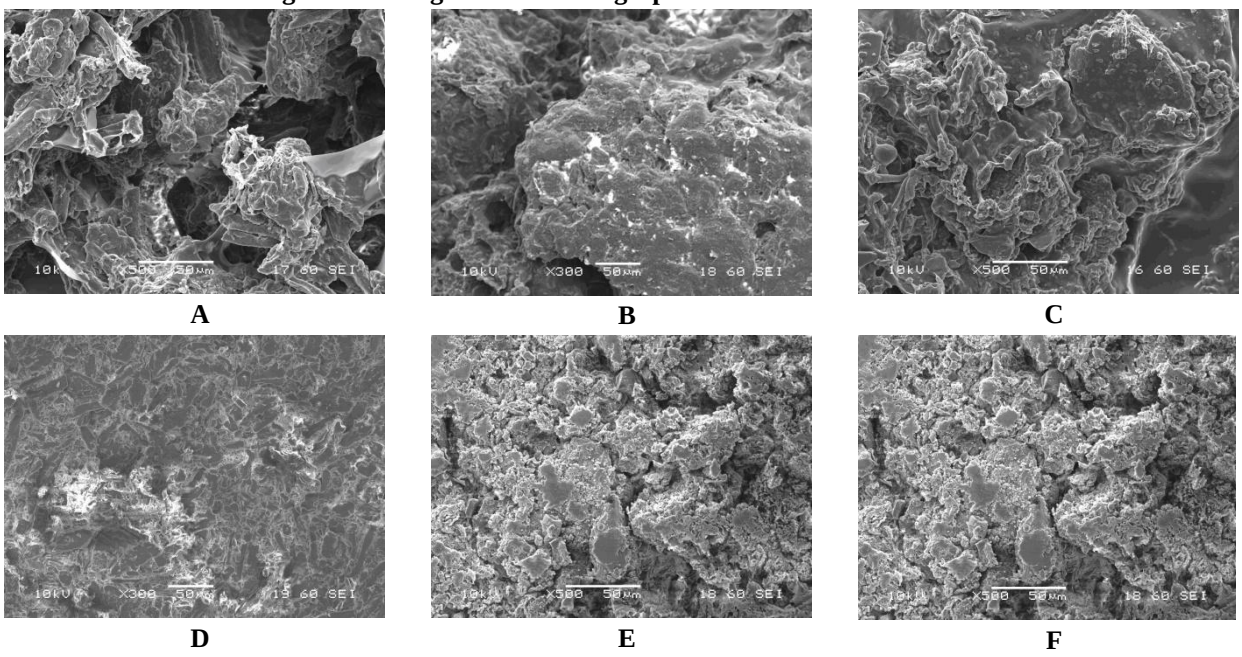
In case of water-soluble drugs, formulation DTZ-M highly sustained the release, showing slower rate of release than formulations with LA and DCP. Along with HPMC, MCC is also swellable diluent and therefore the matrix formed by swelled HPMC and MCC is relatively quite stronger and dense, allowing only diffusion of dissolved drug from the core leading to decreased release rate. Tablets with lactose (DTZ-L) show faster release than tablets with MCC and DCP. Due to the hydrophilicity of both lactose and drug, medium rapidly infiltrate in the tablet dissolving and releasing of drug by both erosion and diffusion. The release being only sustained due to swelled HPMC. In formulation DTZ-D, DCP controls the buffer penetration through HPMC matrix by forming hydrophobic layer and reducing the drug release rate significantly. In this case the drug is released only due to slow swelling and erosion of outer layer of matrix tablet. Though HPMC swells, interparticulate hydrophobic DCP causes incomplete matrix formation and relatively faster erosion.

The characteristic values of the kinetic model were calculated by fitting the dissolution data in PCP disso software (V3, Poona College of Pharmacy, Pune, India.). The dissolution data exhibited a good fit in the model with the value of exponent, *n*, for HPMC matrices being more than 0.45 suggesting diffusion-controlled mechanism in which the rate of diffusion of the liquid is much less as compared with the rate of relaxation of the polymer segment[16,17]. The best fit model for MCC and DCP with DTZ was found to be Higuchi matrix with r = 0.9993 (n = 0.5296) and r = 0.9942 (n = 0.5173), respectively while for lactose best fit model is Peppas r = 0.9976 (n=0.5080) indicating the release controlled by diffusion and erosion being assisting mechanism. The difference in release constants for Higuchi and Peppas was very negligible indicating involvement of both diffusion and erosion mechanism in release the slight higher values predicting the predominance of one on other.

Hydrophobic drug shows slow rate of release, its release rate again modulated by added diluents. Formulations DFS-M, DFS-L, DFS-D shows negligible release in pH 1.2 buffer for 2 hours due to insolubility of drug in that buffer medium. Formulation DFS-M shows very slow drug release due to increased swelling time of MCC and HPMC because the hydrophobic drug reduces the medium infiltration in matrix and drug is released slowly by diffusion and erosion [18]. The SEM after dissolution (**Fig. 2 A)** shows nonuniformly eroded surface. The faster erosion of HPMC and subsequent dissolution of drug results in formation pores.

Formulation DFS-L shows higher release rate as compared to other formulations as hydrophilic LA helps to rapid medium infiltration by creating large pores in tablet matrix bringing comparatively fast swelling of HPMC followed by rapid erosion of matrix (**Fig. 2 B**). A very small portion of tablet was remained after dissolution process due to extensive erosion of formulation.

Fig. 2: Scanning electron micrographs of tablets after dissolution



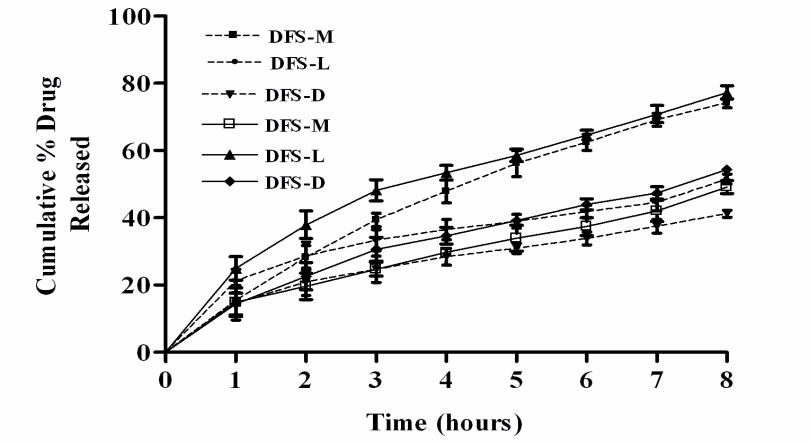
(A) DFS-M-HPMC (B) DFS-L-HPMC (C) DFS-D-HPMC (D) DFS-M-EC (E) DFS-L-EC (F) DFS-D-EC

In formulation DFS-D, hydrophobic drug and DCP highly affected the drug release showing decreased rate of drug release. Due to very slow wetting and pervading of medium, the swelling of HPMC was very slow and also tablet eroded very slowly. Thus reduced rate of swelling and erosion due to higher hydrophobic content resulted in lowered drug release rate (**Fig. 2 C**).

The best fit model for MCC and DCP with DFS was found to be Peppas with r = 0.9790 and r = 0.9705, respectively indicating the release controlled by diffusion and erosion being facilitating mechanism[19]. Lactose abides by zero order release kinetics with r=0.9497 due to faster permeation of medium in to matrices forming pores and increasing erosion and subsequent solublisation of drug. The constant gel layer thickness due to concurrent swelling and erosion of polymer maintains smooth drug release unaffected by drug concentration.

The DFS shows pH contingent solubility towards higher pH values and shows very low initial drug release in first two hours in 1.2 pH HCl. The entrapment of acidic medium in the matrices creates acidic microenvironment and can affect release of drug in pH 6.8 buffer followed after 2 hours in acidic medium[20,21]. This effect was evaluated by carrying out dissolution of same formulations directly in pH 6.8 phosphate buffer. In this case the tablets showed uniform release pattern, releasing about 14-25 % drug in first hour **(Fig. 3)**. These same formulations show less than 10% drug release in first hour after initial 2 hours dissolution at 1.2 pH HCl. After this initial lag period though the release is uniform thereafter. In vivo, dosage form has to be in acidic environment of stomach for nearly 1-2 hours thus creating acidic microenvironment in formulation[22]. Therefore dissolution of sustained release formulations carried out in 1.2 pH for first two hours and then in other relevant pH conditions could give precise prognostications of drug release considering the effect of acidic microenvironment on release rate.

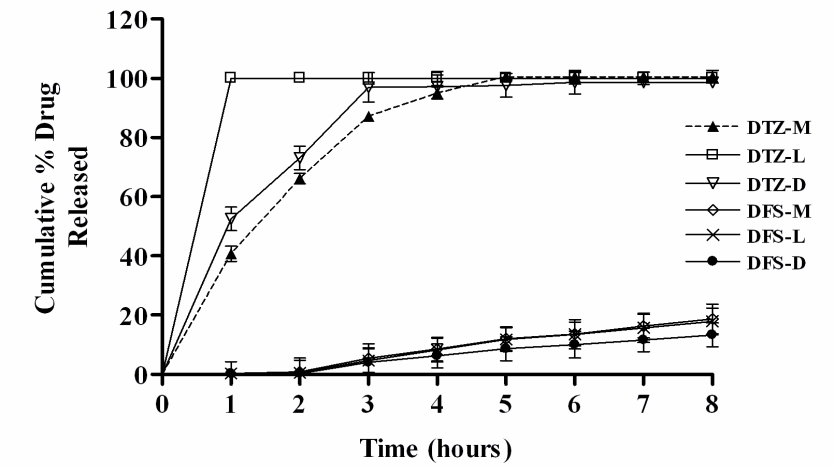
Fig. 3: *In-vitro* drug release from (1) (—) HPMC-DFS (2) (----) EC-DFS tablets with individual diluents directly in pH 6.8 buffer



3.6.2. *In-vitro* drug release from hydrophobic polymer matrix

In-vitro drug release profile of both the drugs from EC matrix is shown in **Fig. 4.** In case of hydrophobic polymers the eluting medium dissolves the drug forming porous network or erodes the drug and polymer from surface[23,24]. EC at 5% concentration is ineffective to sustain the hydrophilic drug release up to 8 hours. Formulation with DTZ-M sustained the drug release up to only 5 hours at this level. High solubility of drug enables fast media infiltration followed by swelling of MCC that builds prominent pores in EC matrix without breaking of tablet, drug gets readily released from these pores. In case of formulation DTZ-L tablets get completely disintegrated within 1 hour giving burst release therefore release kinetics was irrelevant. Used concentration of EC is unable to dissent the medium infiltration in tablet matrix due to eminent hydrophilicity of lactose and drug and itself act as a disintegrant owing to undissolved particles of it reticulated in between LA and DTZ facilating tablet breakdown. Formulation with DTZ-D sustained the drug release up to 6 hours. Drug release is also sustained due to hydrophobic DCP. Hydrophilic drug creates the pores and tablet matrix gets eroded slowly[25-28].

Fig. 4: *In-vitro* drug release from tablets with EC matrix



When dissolution was carried out using pH 1.2 HCl for first 2 hours and thereafter in pH 6.8 phosphate buffer, DFS was released only up to 20% in 8 hrs. As drug is poorly soluble and forms uniform matrix with hydrophobic polymer, it develops high resistance to wetting by medium, resulting in very low rate of drug release. Formulation DFS-M and DFS-L shows nearly similar release rate. DFS-D released drug with relatively slower rate than DFS-M and DFS-L In formulations DFS-M dissolution media slowly penetrates the matrix causing swelling of MCC, because of this ethyl cellulose molecules get separated resulting in slow diffusion of drug and slower erosion of matrix (**Fig. 2 D**). In formulation DFS-L water soluble lactose brings pore formation, which helps to drug release by erosion and diffusion (**Fig. 2 E**). In this case, the tablet mass remained after dissolution is smallest of EC matrices and very porous on visual observation. The drug released initially with erosion as there was no observable size

change for first three hours after that erosion was quite fast and can be noticed. In formulation with DFS-D both the drug and diluent contribute in retarding drug release. Even after prolonged time, drug is released by very slow erosion in pH 6.8 buffer[29]. The tablet was nearly of same size before and after dissolution and was showing least amount of pores on visual observation (**Fig. 2 F**). The best-fit model for MCC, DCP and Lactose with DFS was found to be zero order with *r*=0.9742, 0.9721 and 0.9701. The drug released after 8 hours less than 20% in all the three cases and might not be affected by drug content showing zero order release.

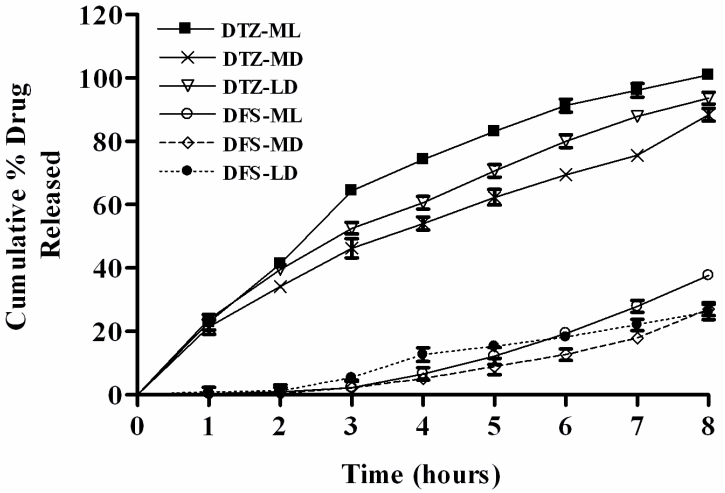
If dissolution is carried out directly in pH 6.8 buffer, it shows drug release up to 65 % in 8 hrs due to pH dependent solubility of drug and polymer **(Fig. 3)**. In this case DFS-M shows higher release rate than both the DFS-L and DFS-D. The possible reason for this is cited in earlier section.

3.7. Effects of combination of diluents on sustained release drug profile

3.7.1. Effects on drug release from hydrophilic matrix

Use of combination of diluents in equal ratio (1:1) shows increased drug release rate in case of freely soluble drug as compared to use of single diluent. Sparingly soluble drug have slow release rate as compared to freely soluble drug (**Fig. 5**).

Fig. 5: *In-vitro* drug release of HPMC tablets with combinations of diluents

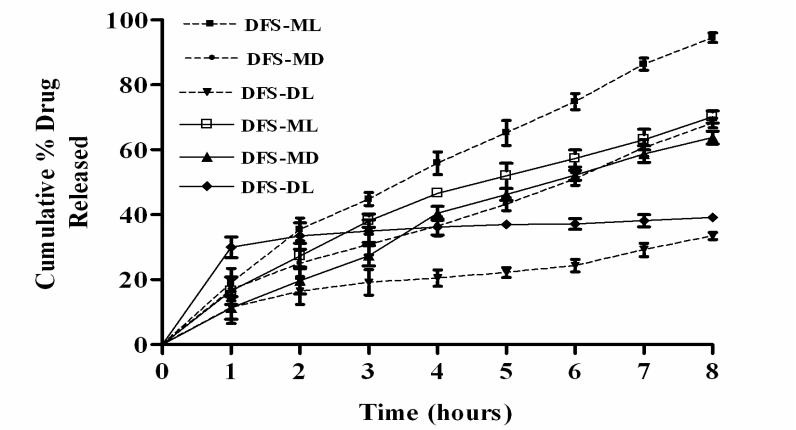


In case of DTZ formulations with MCC and LA, higher solubility of drug and lactose brings faster medium penetration leading to rapid swelling of MCC and HPMC and results in higher release rate as compared to other combinations. In formulation with MCC and DCP only drug is water-soluble and forms surface pores helping in medium penetration causing swelling of MCC and HPMC followed by erosion due to DCP, which is slower as compared to others. In formulation with LA and DCP, freely soluble drug and LA brings rapid swelling of HPMC by medium along with fast erosion of DCP causing rapid breakage of tablet resulting in quite faster release. The best-fit model for MCC, Lactose and DCP with DFS was found to be Peppas with *r*=0.9853 (n= 0.7200, 0.9987 (n= 0.6632) and 0.9988 (n=0.6568). The release model indicates the diffusion and erosion as releasing mechanism. From the n values it can be supposed to be an anomalous or complex behavior in which the rate of diffusion of the liquid and that of swelling are of the same magnitude resulting in both mechanism of release coming into play.

In case of DFS, formulations with MCC and LA shows high release rates as compared to other combinations, in that soluble LA forms pores brings media infiltration causing swelling of HPMC followed by rapid erosion of drug supported by hydrophilic nature of MCC. MCC-Lactose combination shows faster release than MCC alone and slower release than Lactose alone.

Combination of MCC with DCP and LA with DCP has similar drug release rates. MCC-DCP combination shows similar release as in case of MCC alone but shows slower release than DCP alone. DCP-LA combination shows slower release than DCP and Lactose alone, this might be due to faster erosion with DCP alone and in combination lactose dissolves fast allowing swelling of HPMC decreasing drug release. In tablets with MCC and DCP, due to absence of any soluble material medium infiltration was very slow while in tablets with LA and DCP, soluble LA creates pores bringing wetting of surface but as drug and DCP both are hydrophobic hinder the rapid swelling of HPMC these results in slow drug release. **(Fig. 6)**

Fig. 6: *In-vitro* drug release from (1)(──)HPMC-DFS (2)(------)EC-DFS tablets with combination of diluents directly in pH 6.8 buffer

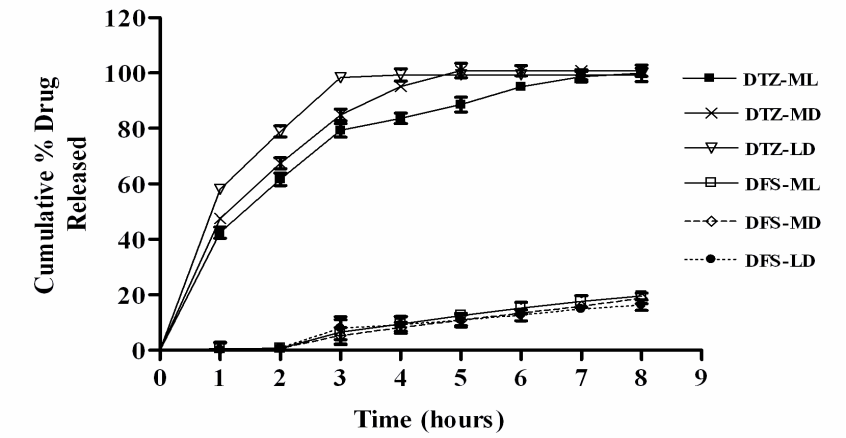


The best fit model for MCC-Lactose and MCC-DCP combination is Peppas with correlation coefficient, r=0.9883 and 0.9748, respectively and the time exponent, n values are >1 indicative of super case II transport mechanism[30-34]. Lactose-DCP combination shows zero order as best fit model (r=9687).The differences in the r values are negligible in Peppas and zero order.

3.7.2. Effects on drug release from hydrophobic matrix

Surprisingly DTZ tablets with MCC and LA combination sustained the drug release for prolonged time as compared to MCC alone and in other combinations. In this drug and LA forms pores at surface bringing swelling of MCC followed by diffusion of drug. As diffusion path increases rate of drug release decreases with time. Presence of Lactose decreases the rate of erosion and release occurs via diffusion through Fickian transport mechanism (n=0.4112). In combinations of MCC with DCP and LA with DCP drug release rate is same (**Fig. 7)**. MCC-DCP and DCP-lactose combination shows slower release than DCP and LA alone. Decrease in rate of erosion might be reasoned for this behavior[35-38].

Fig. 7: *In-vitro* drug release of EC tablets with combination of diluents



The best fit model for MCC-LA and MCC-DCP combination is Peppas with correlation coefficient, r=0.9814 (n=0.4112) and 0.9594 (n=0.3741), DCP-LA combination shows first order release model fitting (r=0.9738).

When dissolution was carried out in pH 1.2 and 6.8 buffers, formulations with DFS showed slower drug release rate without significant difference in between them but had more difference when dissolution was performed directly in pH 6.8-phosphate buffer[39-40]. Formulation with MCC and LA gave faster release as compared to others **(Fig. 6)**. LA helps in tablet wetting but presence of poorly soluble drug decrease the swelling capacity of MCC by increasing interparticulate distance in MCC due to this it behaves as disintegrant causing fast release. While LA with DCP shows slower release in which hydrophobicity of EC, DCP along with drug decreases the medium infiltration through pores created by hydrophilic LA.

The best fit model for MCC-Lactose and MCC-DCP combination is zero order with correlation coefficient, r=0.9756 and 0.9726, DCP-Lactose combination shows first order 0.9727

4. Conclusions

The type of diluents and polymers used imparts evident effect on tablet properties and release mechanism. The data generated in this study also shows that, the drug release from hydrophobic diluents was less than hydrophilic diluents for soluble and insoluble drugs. HPMC and EC matrices of MCC and DCP reveal similar release profiles with both the drugs. Lactose due to hydrophilicity and solubility demonstrate faster release than individual MCC and DCP formulations. For HPMC tablets with MCC and DCP best fit model was Higuchi whereas for LA HPMC it was Peppas indicating change in size of matrix during dissolution. With 5%EC level, controlling DTZ release for more than 6 hours was not possible with individual use of any diluent, alternatively combination of diluents effectively controlled drug release in EC matrices. Use of lactose along with MCC, instead of increasing release, decreased release as compared to MCC alone in EC matrices while in hydrophilic matrices addition of LA increased release rate. However, a number of critical parameters such as granulation process, tabletting conditions, hardness and porosity of the tablet and compression pressure can substantially affect drug release pattern from different matrices.

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