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Original Research Article

Combination of surfactants with other excipients: Effects on drug release and dimensional changes in matrices

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Abstract

Purpose: *To investigate the effect of polymers and surfactants on drug release, gelling, and dimensional changes of matrices.*
Methods: *Flurbiprofen and propranolol were formulated using different types and ratios of polymers including hydrophilic polymers (sodium carboxymethyl cellulose, CMC), and a hydrophobic polymer (Eudragit RS 100). Both cationic (cetrimide, CET)) and anionic (sodium lauryl sulfate (SLS) surfactants were also used. Dissolution rate, swelling rate, and dimensional changes were investigated in dissolution media mimicking gastrointestinal fluids (pH 1.2 and 7.4).*
Results: *The highest drug release rate was 45 and 78 % for flurbiprofen/RS 100 and propranolol/CMC, respectively. Surfactants have also exerted an additional effect on drug release in that SLS enhanced the release of flurbiprofen (blended with RS 100) by 5 % while CET improved propranolol (CMC by 7 %. Clear wetting, swelling, and gelling were observed in the tablets prepared with CMC. Surfactant has no effect on dimensional changes in the tablets.*
Conclusions: *The release rate of propranolol and flurbiprofen is generally governed by polymer type and drug solubility. Dimensional changes in the tablet matrices are mainly constrained by the type of polymers used.*

Keywords: *Propranolol, Flurbiprofen, Excipients, Surfactants, Dimensional changes*

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INTRODUCTION

The manufacturing of controlled release dosage forms is one of the main goals of the pharmaceutical industry due to their therapeutic advantages over conventional dosage forms, e.g., reduced frequency of drug administration and improved patient compliance [1-2]. The preparation of matrices via direct compression techniques is an attractive method because direct compression has some important advantages including low labor input, dry processing, and simple workflow.

Several researchers have employed this method to prepare controlled release matrices via different excipients as well as hydrophilic and hydrophobic polymers [3-6]. Among the hydrophobic polymers, the acrylic resins Eudragit RL100 and RS 100 have shown good results in the preparation of controlled release matrices containing the slightly soluble flurbiprofen with a

half-life of 3 - 4 hours [7]. The drug release occurs via degradation of the tablets [8-9]. The release of propranolol hydrochloride [9] from these polymers is via pores, crack formation, and disruption of the tablets due to dissolution of drug from the matrices. There is no controlled release because all drug is released in less than four hours.

The inclusion of sodium carboxymethylcellulose (CMC) has been studied by many researchers [4-5, 10]. This polymer plays an important role in drug release from the tablets. The influence of surfactants on controlled release has also been studied in detail [3,6-9]. The effect of these surfactants depends on their solubility [8] as well as whether their concentration is below or above the critical micelle concentration (CMC) of the surfactant [11]. The charge of the surfactant is also used in the matrices and influences the drug release: there is increased drug release when the charge of the polymer is the same as the drug. In contrast, when the surfactant and drug have different charges, there is a decrease in drug release [3]. The wetting ability of the surfactant can also impact drug release: The wettability and solubility of the drug increased as the contact angle decreased—this led to increased drug release [12]. The effect of the surfactants on the swelling rate and dimensional changes has been studied by many researchers [13-14]. The results showed a very limited effect on the swelling of the tablets due to their solubility and wettability effects. The purpose of this study is to investigate the effect of polymers and surfactants on drug release, gelling, and dimensional matrix changes.

EXPERIMENTAL

Materials

The following materials were used to prepare the tablets matrix: flurbiprofen (Drogsan), propranolol HCl and glucose from Arab Pharmaceutical Manufacturing-Jordan (APM), sodium lauryl sulfate and magnesium stearate from BDH, cetrimide from Serva, and sodium carboxymethyl cellulose from FMC. Eudragit RS 100 was sponsored by Evonik. All chemicals were of reagent grade.

Preparation of tablets

Eudragit RS100 was powdered in a ball mill and sieved through a 300µm sieve. The drugs and the excipients were blended for five minutes in a blender. The powders were compressed to prepare 400 mg tablets of flurbiprofen and 300 mg of propranolol hydrochloride in a single punch tablet machine (KorchErweka). The ratio between the diameter and the thickness of the cylindrical flat faced tablets was between 0. 3 and 0.9 cm in the formulation of flurbiprofen and 0.2 – 0.9 cm in the formulations with propranolol HCl. The hardness of the tablets in both formulations was 7 -10 kg as measured by a Schleuniger-2 hardness tester. The composition of the formulations is shown in Table 1.

Kinetic data analysis

The data obtained from the *in vitro* release were plotted according to the kinetic model of zero order, first order, and the Higuchi equation.

Dissolution testing

The *in vitro* drug release from the formulation was estimated using the basket method Erweka, DT 6R Heusentamm, Germany) for all dissolution studies. The tests were performed at 37°C with a rotation speed of 100 rpm using 1000 ml of pH 7.4 phosphate buffer for the formulations with flurbiprofen and a pH of 1.2 for the formulations with propranolol HCl.

Samples were collected every hour and filtered and assayed at 248 nm for flurbiprofen and at 289 nm for propranolol via a double beam spectrophotometer (Systronic 2202).

Table 1: Composition (percentage) of the various formulations

	Batch no.								
Ingredient	***F1***	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***	***F9***
Flurbiprofen	50	50	50	50	50	50			
Propranolol							40	40	40
Eudragit RS 100	25	25	25						
CMC				25	25	25	59	58	58
Cetrimide			1			1			1
SLS		1			1			1	
Magnesium stearate	1	1	1	1	1	1	1	1	1
Glucose	24	23	23	24	23	23			

The mean of three determinations was used to calculate the drug release rate of the formulations.

RESULTS

Dissolution experiments

The results were split into two distinct groups according to the formulated drug (fluribiprofen or propranolol; Table 2). Both drugs have a similar pattern in dissolution data, and different percentages of release were detected (Figure 1 and 2). Flurbiprofen is slightly soluble (Figure 1), and the mean percent of drug release from F1 over 8 hours was 37 %. The use of 1% SLS increased the mean drug release to 45 % (F2), and the incorporation of 1 % CET. increased the mean drug release to 40 % (F3). The mean drug release from F4 over the 8 hours was 32 %, and the addition of 1 % SLS led to a mean drug release increase of 39 % (F5). The addition of 1 % of Cet. increased the mean drug release to 35 % (F6).

Table 2: Drug release(%) from the formulations

	Time (h)							
Batch no.	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***
F1	11	15	19	23	26	29	33	37
F2	14	18	22	27	31	35	40	45
F3	10	15	20	24	29	33	37	40
F4	8	12	15	19	22	26	29	32
F5	11	15	20	23	27	32	35	39
F6	9	12	16	20	23	27	31	34
F7	15	24	31	39	47	54	63	72
F8	16	24	31	38	45	53	61	70
F9	17	27	35	44	53	60	69	78

In the case of freely soluble drug (propranolol), the mean drug release from F7 was 72% over eight hours (Figure 2). The addition of 1% SLS decreased the mean drug release to 70% F8, and the addition of 1% Cet. increased the mean drug release to 78% at 8 hours for F9.

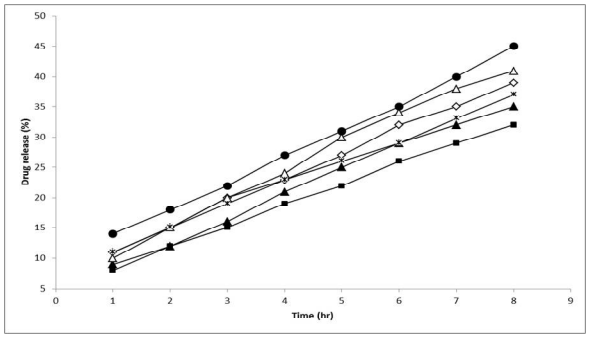

Figure 1: Effect of excipients and surfactants on release rate of flurbiprofen. ***Key:*** F1 (✳), F2 (●), F3 (△), F4 (■), F5 (◇), and F6 (▲), denote different batches

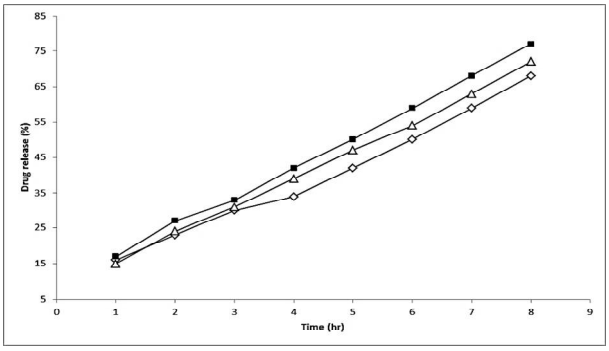

Figure 2: Effect of excipients and surfactants on release rate of propranolol hydrochloride. ***Key:*** F7 (△), F8 (■), and F9 (◇), denote different batches

Swelling and dimensional changes

No dimensional changes in the matrices F1 to F3 were observed when the tablets were placed in pH 7.4 dissolution medium for hours; however, the tablets did become smaller. Formulations with hydrophilic polymers with flurbiprofen (F4 to F6) swelled somewhat, but the tablets retained their shapes (Figure 3 A, B and C). On the other hand, formulations with hydrophilic polymers and propranolol (F7 to F9) swelled first and then deformed losing their shapes after 4 h; they subsequently cracked and disintegrated (Figure 4 A, B and C).

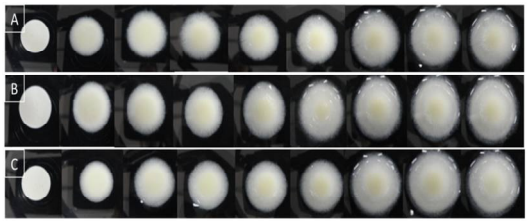

Figure 3: Effect of NaCMC and hydrophobic drug flurbiprofen on the swelling rate and dimensional changes of the matrices in pH 7.4 phosphate buffer. (**A**) Batch F4 (without surfactant). (**B**) Batch F5: The effect of anionic surfactant (SLS). (**C**) Batch F6: The effect of cationic surfactant (CET)

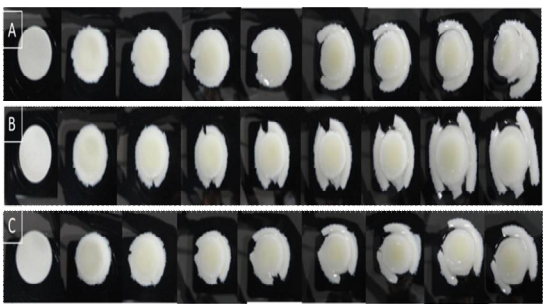

Figure 4: The effects of NaCMC and the soluble drug propranolol on the swelling rate and the dimensional changes of the matrices at pH 1.2. (**A**) Batch F7. (**B)** Batch 8: Teffect of anionic surfactant (SLS). (**C**) Batch no. F9: effect of cationic surfactants (CET)

Table 3: Drug release kinetic data

Batch no.	Zero order			First order			Higuchi		
	r^2	*Slope*	*Intercept*	r^2	*Slope*	*Intercept*	r^2	*Slope*	*Intercept*
F1	0.994	0.345	-2.403	-0.997	-0.018	1.992	0.995	0.085	0.41
F2	0.996	0.165	-1.554	-0.998	-0.03	1.965	0.992	0.046	0.559
F3	0.991	0.189	-1.899	-0.996	-0.03	1.981	0.996	0.76	0.354
F4	0.989	0.145	-1.905	-0.993	-0.062	1.964	0.988	0.056	0.47
F5	0.992	0.278	-1.876	-0.991	-0.043	1.99	0.997	0.048	0.345
F6	0.997	0.169	-2.071	-0.993	-0.057	1.96	0.982	0.035	0.477
F7	0.982	0.141	-1.969	-0.987	-0.062	1.97	0.987	0.062	0.472
F8	0.992	0.289	-2.013	-0.986	-0.062	1.99	0.978	0.038	0.488
F9	0.995	0.165	-1.573	-0.991	-0.071	2.11	0.983	0.033	0.491

Kinetic assessment of drug release

The dissolution data could be zero order or first order, and analysis via the Higuchi equation is presented in Table 3. Good linearity was observed for all formulations suggesting that the drug release from the tablets occurred via two mechanisms—diffusion and erosion of the matrices at the specified time.

Contact angle

Contact angle data are listed in Table 4.

Table 4: Contact angle as a function of formulation

Formulation	Contact angle (^{o})
No surfactant	63
SLS	54
CET	62

DISCUSSION

In general, the rate of drug release depends on the drug solubility and the chemical nature of the polymer [17]. This study investigated the rate of release of two different model drugs: propranolol and flurbiprofen. Propranolol is six-fold more water soluble than flurbiprofen—it is better at forming hydrogen bonding than flurbiprofen.

The incorporation of the hydrophilic and hydrophobic polymers as well as other excipients into the matrices of flurbiprofen and propranolol modified the drug release (Table 2 (F1, F4, F7) and Figures 1 and Figure 2). The slower drug release in F1 may be because flurbiprofen and the acrylic resin RS 100 are poorly water soluble [18,19]. Their presence restricted the penetration of the dissolution medium into the tablets [8]. The addition of water-soluble excipients (i.e., glucose) may enhance the release rate [7]. However, the addition of glucose to F1 was not sufficient to enhance the dissolution rate. Thus, the drug release may be explained by attrition and diffusion (Table 2 and Figure 1).

The solubility of the drug in the matrices prepared here has a crucial effect on the drug release; thus, we compared the release of F4 and F7 that have the same excipients but different formulated drugs. The percent of drug release in F7 was double that of F4. This difference may be because of the slight solubility of flurbiprofen [7] and the swelling ability of CMC. This swelling accommodates extra drug cargo within the matrices without breaking the links of the polymer or altering the shape of the matrix during dissolution.

The swelled matrices subsequent delayed and regulated the drug release from the tablets (Table 1 and Figure 1). The high percent of drug release from F7 is due to the amount of water-soluble propranolol in the formula. Furthermore, the reduced stability of the CMC and weaker matrix led to tablet rupture (Table 2 and Figure 2).

The incorporation of surfactants (anionic and cationic) in pharmaceutical preparations can modify drug release [6,8,9].

Table 5: Release profile of formulations relative to USP pharmacopoeia guidelines [20]

Time (h)	US Pharmacopoeia requirement for drug release	Drug release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Not more than 25%	11	14	10	8	11	9	15	16	17
4	Between 20% and 40%	23	27	24	19	23	20	39	38	44
8	Between 40% and 60%	37	45	40	32	39	34	72	70	78

The charge of the surfactant also plays an important role in modifying drug release from the matrices. The enhancement in drug release was clear when the anionic surfactant was incorporated within the matrices F2 and F5 (Table 2 and Figure 1). The increase in drug release may be due several reasons: 1) free soluble surfactant (1 g /10 ml) [7]; 2) incorporation of glucose with SLS increased the number of pores within the tablets; 3) the anionic model drug (flurbiprofen) with the anionic surfactant increased the release rate of drug; 4) the wettability effect of SLS [8]—the wettability is always correlated with the contact angle. Thus, the enhanced wettability of SLS increased the dissolution rate (Table 4).

In the case of the cationic surfactant, the increase in drug release after the addition of Cet. (F6) may be due to one or all the following reasons: 1) the high solubility of the surfactant (1 in 2) [7]; 2) the presence of glucose and Cet. That increased the number of pores within the tablets to increase the drug release; and/or 3) the wettability effect of Cet. (Table 2 and Figure 1).

However, the effect of SLS (F2) on drug release is more than Cet. (F3). This may be because SLS is more hydrophilic than Cet. Thus, there is repulsion of the anionic charge between SLS and flurbiprofen. Anionic surfactants have been used with cationic drugs to reduce drug release [15]. We saw this for Cet. Similar results were observed for propranolol formulations [F8, F9].

Formulations F2, F3, and F5 were shown to offer controlled release by comparing the percentage of drug release to the USP Pharmacopoeia guidelines.

Swelling, gelling, and table morphology changes can indicate penetration of the dissolution medium into the tablets. This modulates drug release from the swollen matrices [14]. Consequently, hydrophilic polymers appear to be the appropriate vehicle for the preparation of various oral controlled drug release preparations [21]. The increase in the swelling and the dimensions of the flurbiprofen formulations from F4 to F6 may be attributed to the presence of CMC within the formulation as well as drug hydrophobicity [22] (Figures 3A, B, and C). F7 to F9 used the hydrophilic polymer CMC—here, the soluble drug caused rapid swelling and subsequent rupture of the tablets due to the extreme penetration of the dissolution medium into the matrices.

CONCLUSION

Drug release of both model drugs (flurbiprofen and propranolol) are governed by drug solubility as well as type of surfactant and polymer (hydrophobic and hydrophilic). Drug release correlates with the drug's water solubility and wettability by the surfactant. An oppositely charged surfactant and drug reduces the rate of release. The hydrophilicity of the polymer is inversely proportional to drug release. Thus, the findings of this research offer a better understanding of the interaction of excipients with drug release, which should promote a better formulations approach.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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REFERENCES

1. *Lachman L, Lieberman H, Kanig J. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger; 1986; p 430.*

2. Efentakis M, Al-hmoud H, Choulis NH. Effect of additives on Flurbiprofen controlled release preparation. Acta Pharm Technol 1990; 36(4): 237-239.
3. Al-Hmoud H, Ehab IE, Nasser EI Attia OA, Eldessoky SD. Formulation of propranolol HCl controlled release tablets: effect of surfactant charge and mechanism of drug release. Afr J Pharm Pharmacol 2014; 8(43): 1110-1117.
4. Al-Hmoud H, Efentakis M, Choulis NH. A controlled release matrix using a mixture of hydrophilic and hydrophobic polymers. Int J Pharm 1991; 68(1): R1-R3.
5. Bavega SK, Ranga KV, Puri PK. Zero order release hydrophilic matrix tablets of β- adrenergic blockers. Int J Pharm 1987: 3939-3945.
6. Dredan J, Zelko R, Bihari E, Racz I, Gondfar E. Effect of polysorbates on drug release from wax matrices. Drug Dev Ind Pharm 1998; 24(6): 573-576.
7. Martindale W, Reynolds J. Martindale: The Extra Pharmacopoeia. 31st ed. London: The Pharmaceutical Press; 1996. P. 936-937.
8. Efentakis M, Al-Hmoud H, Buckton G, Rajan Z. The influence of surfactants on drug release from a hydrophobic matrix. Int J Pharm 1991; 70(1): 153-158.
9. Nokhodki A, Daoud HZ, Farnaz MZ, Nita TZ. The effect of various surfactants and their concentrations on controlled release of captopril from polymeric matrices. Acta Pharm 2008; 58(2): 151-162.
10. Alhmoud H, Alhmoud D. The Effect of Polymers Composition on the Release of Drug from Controlled Release Tablets. Lat Am J Pharm 2019; 38(2): 323-8.
11. Al-Hmoud H. Formulation of propranolol HCl controlled release tablets: effect of surfactant charge and mechanism of drug release. Afr J Pharm Pharmacol 2016; 10(8): 88-84.
12. Sinko RPh, Patrick J. Martins Physical Pharmacy and Pharmaceutical Sciences. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2011; p 398.
13. Efentakis M, Vlachou M, and Choulis N H. Effect of Excipients on Swelling and Drug Release from Compressed Matrices. Drug Dev Ind Pharm 1997; 23(1):107-112.
14. Vlachou M, Hani N, M Efentakis, Tarantili P A, Andreopoulosms G. Polymers for used in controlled release systect of surfactants: the effect of surfactants on their swelling properties. J Biomater Appl 2000; 15(1): 65-77.
15. Feely LC, Davis SS. The influence of surfactant on drug release from hydroxypropyl methylcellulose matrices. Int J Pharm 1988; 41(1): 83-90.
16. Al-Hmoud H, Ibrahim NE, El- Hallous I. Surfactant solubility, concentration and other formulation effect on drug release rate from a controlled release matrix. Afr J Pharm Pharmaco 2014; 8(13): 364–371.
17. Savjani K, Gajjar A, Savjani J. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm 2012; 2012: 195727.
18. Daravath B, Naveen C, Vemula S, Tadikonda R. Solubility and dissolution enhancement of flurbiprofen by solid dispersion using hydrophilic carriers. Braz J Pharm Sci 2018; 53(4): 1-10.
19. Gade R, Murthy T. Effect of hydrophilic and hydrophobic polymers on release kinetics of metoprolol succinate extended release tablets. Asian J. Pharm 2011; 5(2): 101-106.
20. Singh D, Baier R. Contact Angle and Wettability Correlations for Bioadhesion to Reference Polymers, Metals, Ceramics and Tissues. Advances in Contact Angle, Wettability and Adhesion. Lublin: Wiley; 2018; pp 349-372.
21. Palmer D, Levina M, Nokhodchi A, Douroumis D, Farrell T, Rajabi-Siahboomi A. The Influence of Sodium Carboxymethylcellulose on Drug Release from Polyethylene Oxide Extended Release Matrices. AAPS Pharm Sci Tech 2011; 12(3): 862-872.