OPTIMIZATION OF COMPRESSED GUAR GUM BASED MATRIX SYSTEM: INFLUENCE OF FORMULATION ON CHANGE OF DRUG(S) RELEASE RATE

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ABSTRACT

The significance (effect) of factors such as drug solubility, proportion of polymers and other additive on drug release from guar gum based matrix system was investigated. Pseudoephedrine HCl, Metformin HCl, Tetracycline HCl and Diclofenac sodium with solubilities > 50 %, $\leq$ 50 %, $\leq$ 10 %, < 0.1 % respectively were used as drug models. The release rate and mechanism changed with formulation. Guar gum content was the predeterminant controlling factor. As the guar gum content was increased, drug release rate was decreased. When the guar gum and drug proportion was constant, change in the rate of drug release was observed with the change in the drug solubility. Additive effects were also examined. Changing from insoluble to soluble excipients saw an increase in drug release for all solubilities of drugs. Finally the rate of dynamic swelling and the dissolution of the polymer matrix on the release mechanism are discussed. This formulation approach allows us to optimize the compressed guar gum based matrix formulations at the development stage.

Keywords: Guar gum, Diclofenac Na, Metformin HCl, Pseudoephedrine HCl, Tetracycline HCl.

INTRODUCTION

The natural hydrophilic polymer guar gum has been widely used recently to control drug release from solid dosages, such as from sustained release or controlled release system. In vitro and in vivo release of the highly soluble drug (Diltiazem) and insoluble drug (Ketoprofen) from guar gum matrix tablets was found to be similar to that of commercial product[1, 2]. The same group of scientists also found that guar gum formulations were relatively insensitive to changes in stirring speed during in vitro dissolution testing and the dissolution profile were not significantly affected by changes in compaction pressure or by storage under accelerated stress conditions.

Drug release can be affected by several factors including the physiochemical properties of drug molecule, proportion of the polymer used and additives. The effect of those factors on drug release would mostly be due to expansion of gel barrier formulations of continuous gel formation.

Little attention has been directed to the effects of the parameters, polymer proportion, physical properties of the drug and the type of additives in manufacturing parameters a formulation on the release of drug from guar gum based matrix tablets. This is of particular importance as the studies would enable to modulate release kinetics. Four drugs of different solubilities e.g. Pseudoephedrine HCl (625 mg/ml), Metformin HCl (500 mg/ml), Tetracycline HCl (100 mg/ml) and Diclofenac sodium (10 mg/ml) were chosen as model drugs.

MATERIALS AND METHODS

Pseudoephedrine HCl (Zim laboratories, Nagpur, INDIA), Metformin HCl (Warner Laboratories, Hyderabad, INDIA), Diclofenac Na (Aarti Drugs Ltd, Hyderabad, INDIA), Tetracycline HCl (Relief lab, Nagpur, INDIA)

Matrix tablet preparation:

Matrices of Pseudoephedrine HCl, Metformin HCl, Tetracycline HCl and Diclofenac sodium with guar gum and/or additives as shown in (Table 1) were thoroughly mixed in mixing bag for 10 minutes. Granules of the mixes prepared by moist granulation technique were weighed and fed manually into the die of single punch tablet machine (Kilburn, type-3) using flat punches of diameter 11 mm.

Table 1: Formulations of model drugs considering different proportion of guar gum.

Formulation	PF1	PF2	PF3
Pseudoephedrine HCl	120 mg	120 mg	120 mg
Guar gum	120 mg	360 mg	480 mg
Magnesium Stearate (1%)	0.01	0.01	0.01
Formulation	**TF1**	**TF2**	**TF3**
Tetracycline HCl	250 mg	250 mg	250 mg
Guar gum	250 mg	150 mg	83 mg
Magnesium Stearate (1%)	0.01	0.01	0.01
Formulation	**MF1**	**MF2**	**MF3**
Metformin HCl	500 mg	500 mg	500 mg
Guar gum	250 mg	375 mg	500 mg
Magnesium Stearate (1%)	0.01	0.01	0.01
Formulation	**DF1**	**DF2**	**DF3**
Diclofenac	100 mg	100 mg	100 mg
Guar gum	100 mg	80 mg	40 mg
Magnesium Stearate (1%)	0.01	0.01	0.01

(Key: PF- Pseudoephedrine HCl, TF- Tetracycline HCl, MF- Metformin HCl, DF- Diclofenac Na)

Dissolution studies

Tablet batches were subjected to dissolution study at 37°C and 50 rpm, with USP 23 dissolution apparatus 2 (paddle method) in 900ml of 6.8 pH phosphate buffer. Samples (5ml) at predetermined time intervals were withdrawn, filtered and analyzed spectrophotometrically at a wavelength of 257 nm, 276 nm, 232 nm, 357.5 nm for Pseudoephedrine HCl, Diclofenac sodium, Metformin HCl, Tetracycline HCl respectively. Fresh dissolution medium (5 ml) was added to the bath to maintain constant volume. Each experimental work was done in triplicate (n=3).

RESULTS AND DISCUSSION

There must be sufficient polymer to gum ratio in a matrix system to form a uniform barrier for drug release. This barrier protects the drug from immediate releasing in the dissolution medium with increase in the guar gum level, the release of entire four models drugs from their respective compressed formulation decreased [Fig. 1(A,B)]. This may be explained by the swelling of granules after it absorbed water. A higher amount of gum absorbs more water and causes greater swelling, thus increasing the length of drug diffusion path leading to decrease in the amount of drug [3, 4].

Table 2: Physical properties of model drugs considering different proportion of guar gum.

Drug	Pseudoephedrine HCl			Metformin HCl		
Formulation	PF1	PF2	PF3	MF1	MF2	MF3
Hardness	2.1+0.2	2+0.26	5.5+0.21	2+0.2	2.5+0.44	4+0.22
Friability	2+0.21	0.75+0.51	0.55+0.32	2.4+1.6	2.2+1.8	1.08+0.11
Drug	Tetracycline HCl			Diclofenac Na		
Formulation	TF1	TF2	TF3	DF1	DF2	DF3
Hardness	4+0.17	5.5+0.21	5.4+0.1	3.8+0.1	4.5+0.2	5+0.2
Friability	0.97+0.32	0.57+0.28	0.41+0.43	0.98+0.18	0.36+0.12	0.33+0.2

(Key: PF- Pseudoephedrine HCl, TF- Tetracycline HCl, MF- Metformin HCl, DF- Diclofenac Na)

It was interesting to note that proportion of gum used in the formulation shows direct influence on the physical properties of the matrix tablets of the drugs (Table 2). This effect was more prominent with the water soluble drug pseudoephedrine HCl and metformin HCl. On the contrary the proportion of gum has little effect on the physical properties of the compressed guar gum matrix containing less water soluble drug Tetracycline HCl and Diclofenac sodium.
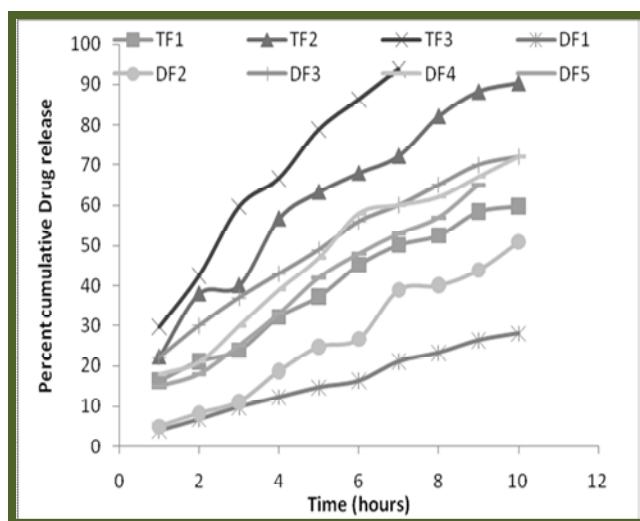

Figure 1(A): Rate of release of model drugs considering different proportion of guar gum
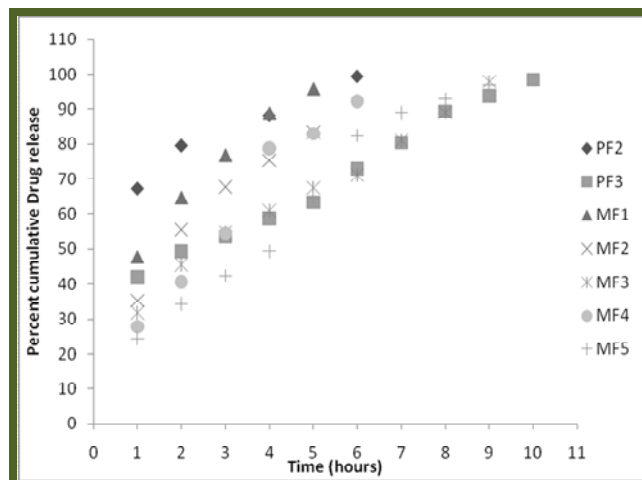*(Key: TF- Tetracycline HCl, DF- Diclofenac Na)*

Figure 1(B): Rate of release of model drugs considering different proportion of guar gum
(Key: PF- Pseudoephedrine HCl, MF- Metformin HCl)

Effect of drug solubility on release behavior

The effect of drug solubility on release kinetics was also investigated. The physicochemical properties of model drugs used are provided in Table 3. As shown in Fig. 1 (A, B), to sustained the drug over 8 hours the proportion of gum required changes from more to less for water soluble drug to water insoluble drug. However when gum and drug proportion was constant, change in the percent drug release was observed with the change in the solubility of the drug (Fig.2). At constant drug: guar gum proportion, as the solubility of the drug change from water soluble

metformin HCl to insoluble diclofenac sodium, the total percent drug release decreases from the 60% to 15% respectively in 5 hours. The observed effect may be attributed to both slow dissolution of diclofenac Na and less number of voids present in the matrix tablet that delay liquid penetration. On the contrary matrix tablet of high water soluble drug might be resulting in to the high porous matrix that allows greater water penetration thus enhancing the swelling of matrix and drug dissolution[5]. These results of the effect of the drug solubility were consistent with reported results on ether cellulose, another swellable matrix former[6].

Table 3: Physico-chemical characteristics of model drugs used for preparation of matrix tablet (SR)

Drug	Molecular Wt.	Melting Point (°C)	Solubility	$t_{1/2}$	Stability of drug
Pseudoephedrine HCl	201.7	214	625 mg/ml	5.8 H	Hygroscopic
Metformin HCl	165.6	225-232	500 mg/ml	1.5 H	Stable
Tetracycline HCl	480.9	182-186	100 mg/ml	9 H	Stable
Diclofenac Na	318.1	283-298	10 mg/ml	5-6 H	Stable

Table 4: Formulation of model drugs considering water soluble and water insoluble additives

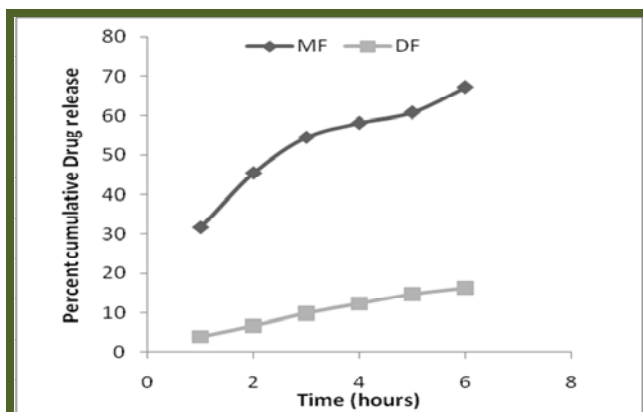| Content	DF3	DF4	DF5	Content	MF4	MF5
Diclofenac Na	100 mg	100 mg	100 mg	Metformin HCl	500 mg	500 mg
Guar gum	40 mg	40 mg	40 mg	Guar gum	500 mg	500 mg
Lactose	-	80 mg	-	Lactose	80 mg	-
DCP	-	-	80 mg	DCP	-	80 mg

(Key: MF- Metformin HCl, DF- Diclofenac Na)

Figure 2: Percent drug release for Metformin HCl (MF) and Diclofenac Na (DF) at constant drug: guar gum proportion.
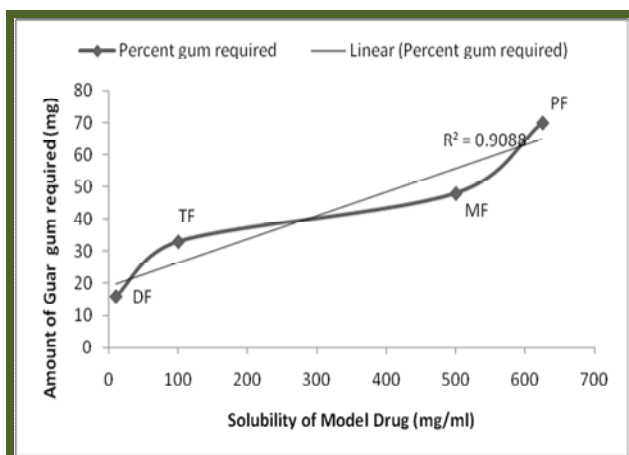

Figure 3: Amount of guar gum required considering solubility of model drug in water.
(Key: PF- Pseudoephedrine HCl, TF- Tetracycline HCl, MF- Metformin HCl, DF- Diclofenac Na)

An interesting correlation can be established between the solubility of drug in water and proportion of drug or concentration of guar gum required as shown in Fig.3. The solubility of pseudoephedrine HCl in water is 625mg/ml, metformin HCl is 500 mg/ml, tetracycline HCl is 100 mg/ml and diclofenac sodium is 10 mg/ml and corresponding proportion of gum required is 70%, 48%, 33% and 16% w/w of the total tablet weight respectively. Near to linear relation exists with r2 as 0.9088, which suggests that, if solubility of the drug in water is known the amount of guar gum that that would be required for sustained release formulation for over 10 hour can be approximated.

Effect of additives on release behavior

Additives are often needed to maintain the tablet size or to modify drug release[3]. Drug release characteristics from matrices containing additives were thus examined (Table 4) considering the formulations of Metformin HCl, as water soluble drug and diclofenac sodium, as water insoluble drug. The dissolution profiles are shown in Fig. 4. A common observation was made for the two solubility categories of the drugs, with the incorporation of water soluble lactose additives, the overall percent release of drugs occur more. In contrast the addition of dicalcium phosphate decreases the percent release of drugs. The above difference in the release of drug might be due to the solubility of lactose and their effect on tortuosity[7]. As water soluble diluents dissolves, it diffuses outward and decrease tortuosity for the drugs to release. The water insoluble diluents dicalcium phosphate did not diffuse outward, but become entrapped in the matrix, consequently making drug to release with difficulty.
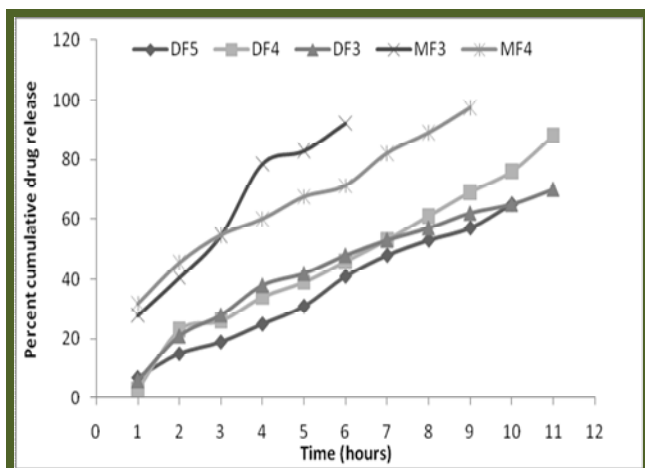
Figure 4: Percent rate of release of model drugs considering water soluble and water insoluble additives *(Key: MF- Metformin HCl, DF- Diclofenac Na)*

CONCLUSION

If the physicochemical characteristics of the drugs such as solubility and the matrix former characteristics are clarified, the dissolution/release of drug and its controlling method can be predicted. Further, if the additive(s) are chosen carefully, it should be possible to balance the release of both water soluble and water insoluble drug at desired rate. This approach might provide us with useful parameters in the development and optimization stage of compressed guar gum base matrix formulations.

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