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## Effect of gums and excipients on drug release of ambroxol Hcl sustained release matrices

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### ABSTRACT

**Objective:** The objective behind present investigation was to formulate matrices of Ambroxol hydrochloride with natural gums like Xanthan, Guar and  $\kappa$ -Carrageenan gum and their combinations in different ratios to develop a sustained release dosage form

**Materials & Methods:** Matrix tablets were formulated using natural gums like Xanthan gum, Guar gum and  $\kappa$ -Carrageenan gum and their combinations at different ratios. The effect of water-soluble and water insoluble excipients on release profiles and matrix swelling in pH 6.8 phosphate buffer was studied and treated with release kinetic models. Accelerated stability studies were conducted as per ICH Guidelines at 40°C/75% RH for 6 months.

**Results and Conclusion:** Xanthan gum and  $\kappa$ -Carrageenan gum retarded the drug release more than Guar gum. The excipients Avicel 102 and Lactose enhanced the dissolution rate whereas Dicalcium phosphate retarded the drug release. Xanthan gum and Carrageenan showed high swelling of matrices. It can be concluded that that natural gums can be effectively used for oral sustained release dosage form.

**Keywords :** Ambroxol hydrochloride, Xanthan gum, Carrageenan gum, Guar gum.

### 1. INTRODUCTION

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as trans-4- [(2-Amino-3, 5-dibromobenzyl) amino]-cyclohexanol. It is an expectoration improver and a mucolytic agent used in the treatment of acute and chronic disorders characterized by the production of excess or thick mucous. (Sweetman et. al. 2002). Its short biological half life (4 h) that calls for frequent daily dosing (2 to 3 times) and therapeutic use in chronic respiratory diseases necessitates its formulation into sustained release dosage form. (Vergin et. al.1985).

For any controlled-release dosage form it is very important to use minimum number of excipients with minimum processing steps in order to reduce the tablet-to-tablet and batch-to-batch variations, hence direct compression is the most suitable and easily up-scalable technique. On contact with an aqueous medium, the hydrophilic polymer matrix gradually begins to hydrate from the periphery towards the centre forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into the aqueous medium (Colombo et. al. 1985; Colombo et. al. 1995). Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. The objective of this study was to develop matrix sustained-release tablets of Ambroxol using natural gums (xanthan, guar and Carrageenan gum) as suitable hydrophilic matrix system.

## 2. MATERIALS AND METHODS

### Materials:

The drug Ambroxol Hydrochloride was procured as gift sample from (Shreya Pharmaceuticals Limited, Aurangabad, India), Xanthan gum, Guar Gum,  $\kappa$ -Carrageenan gum were procured from (Loba Chemicals, Mumbai, India), Avicel PH 102, Dicalcium Phosphate and Lactose were procured from (Emcure Pharmaceuticals, Pune, India). All other chemicals were purchased and were of analytical grade.

### Methods:

#### Preparation of Matrices:

Ambroxol hydrochloride, Xanthan, Guar and  $\kappa$ -Carrageenan gum were mixed separately in various ratios individually and in combinations with each other in a laboratory mixer and were passed through 40-mesh screen. Lactose, Avicel 102 and Dicalcium phosphate were used as fillers-binders for the matrices. The formulations prepared are presented in **Table I**. The tablets were compressed by direct compression method by using Multistation Tablet Punching Machine – Karnavati - Minipress D-II Link, Mumbai fitted with 8mm diameter flat-faced punches. For each batch, 50 tablets were compressed.

#### Evaluation of Tablets:

The tablets were also evaluated as per IP1996 for weight variation (N=20), hardness (N=6), thickness (N=20), and friability. Hardness was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test was conducted using Roche friabilator (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier calipers (Mitutoyo Corp, Kawasaki, Japan). Drug content were determined by potentiometric titration.

#### In-Vitro Drug Release Studies:

The release rate of Ambroxol hydrochloride tablets was determined using USP Dissolution Testing Apparatus II. The dissolution test was performed using 900 ml of 6.8 PH Phosphate buffer solution, at  $37 \pm 0.50^\circ\text{C}$  and 100 rpm. A 5ml sample was withdrawn at interval of one hour and replaced with 5ml fresh aliquot; dissolution study was conducted for 12 hrs. The samples were filtered through Whatman filter paper no.41. Absorbance of above samples were measured at 248 nm on UV-VIS spectrophotometer (SHIMADZU UV-3600). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

#### Stability Studies (Mathews et. al. 1999)

Stability studies were conducted on Ambroxol Hydrochloride matrix tablets containing Xanthan, Guar and

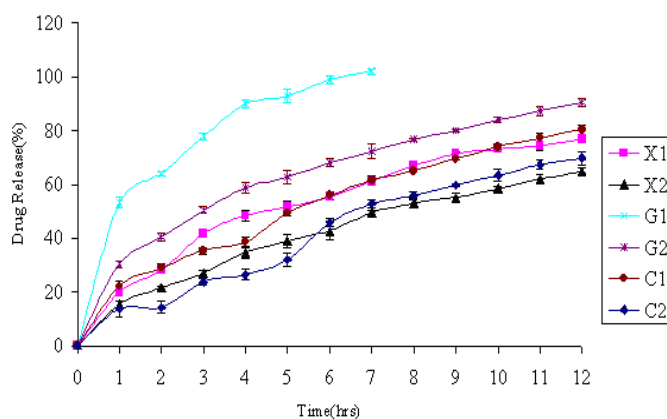
$\kappa$ -Carrageenan gum to assess their stability with respect to their physical appearance, drug content, and drug release characteristics after storing in them Stability chamber (Thermolab) at  $40^\circ\text{C}/75\%(\text{RH})$  for 6 months.

## 3. RESULTS

### Effect of gum type:

The effect of Xanthan gum, Guar gum,  $\kappa$ -Carrageenan gum is shown in **Figure 1**. As the amount of Xanthan gum in the matrix increased, there would be a greater degree of hydration with simultaneous swelling which results in a lengthening of the drug diffusion pathway and reduction in drug release rate. Among the different formulations, **X1** showed highest release of 76.85% in 12 h. Guar gum has minimum water uptake and hence minimum swelling (Al-Saidan *et. al.* 2005). At low concentrations of guar gum (**G1** formulation) a very rapid release of drug is observed. So more quantity of polymer concentration was required to achieve sustained release. In case of  $\kappa$ -Carrageenan gum, among the different formulations **C1** showed release of 80.42% in 12 h. Due to its gelling property, it has been studied as a release retardant for ionic and nonionic drugs (Sipahigil *et. al.* 2001, Picker *et. al.* 1999). Drug release decreases as swelling increases, Carrageenan gum swells rapidly and increases the drug diffusion pathway and hence causes reduction in drug release.

**Fig; 1. Drug Release study of Ambroxol HCl Sustained Release Matrices of individual's gums.**



### Effect of combination of Gums:

Combinations of Xanthan gum and Guar gum at different ratios are shown in Table I. As the amount of Xanthan gum in the matrix increases a greater retardation of drug is observed. This may be due to the greater degree of swelling of Xanthan gum. As shown in Figure 2 when the concentration of Guar gum in the matrix is increased a higher initial release as well as increased drug release for a period of 12h is observed. This is due to the low water uptake of guar gum as compared to Xanthan

**Table-I; Composition of 75 mg Ambroxol HCl Matrices.**

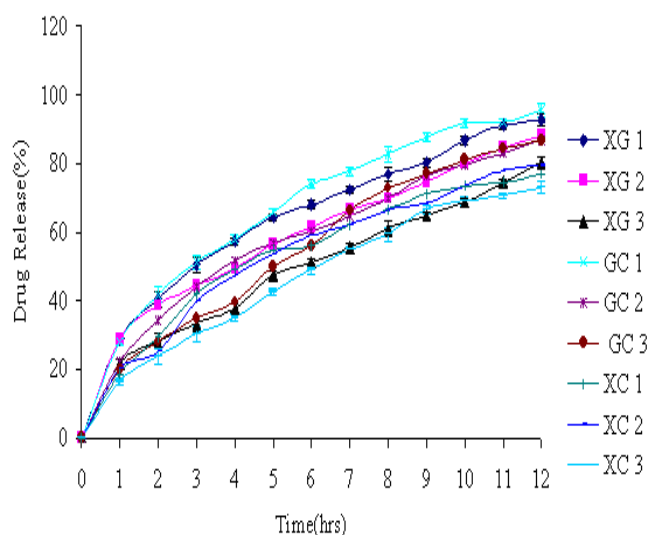
Content/ Formulation	X1	X2	G1	G2	C1	C2	XG1	XG2	XG3	GC1	GC2	GC3	XC1	XC2	XC3
Xanthan gum(X)	75	150	---	---	---	---	37.5	75	112.5	---	---	---	37.5	75	112.5
Guar gum(G)	---	---	75	150	---	---	112.5	75	37.5	37.5	75	112.5	---	---	---
Carrageenan gum(C)	---	---	---	---	75	150	---	---	---	112.5	75	37.5	112.5	75	37.5

**Table-II; Drug Release study of Ambroxol HCl Sustained Release Matrices**

Formulation Code	Zero Order	First Order	Matrix	Peppas	Hixon Crowell	'n' value	Best fit Model	%Release in 12 hrs
<i>X1</i>	0.8651	0.9834	0.9956	0.9921	0.9592	0.5504	Matrix	76.946±3.21
<i>X2</i>	0.9296	0.9895	0.9929	0.9975	0.9767	0.5979	Peppas	64.717±1.22
<i>G1</i>	0.7433	0.9564	0.9802	0.9920	0.9506	0.3534	Peppas	99.45 in 7hr
<i>G2</i>	0.7831	0.9903	0.9950	0.9986	0.9627	0.4399	First Order	90.414±3.14
<i>C1</i>	0.9184	0.9937	0.9960	0.9924	0.9860	0.5503	Matrix	80.266±1.11
<i>C2</i>	0.9783	0.9923	0.9555	0.9752	0.9926	0.7602	Peppas	69.767±3.13
<i>XG1</i>	0.8201	0.9865	0.9977	0.9988	0.9774	0.4658	Peppas	92.622±3.04
<i>XG2</i>	0.8466	0.9863	0.9981	0.9968	0.9739	0.4532	Peppas	88.207±3.45
<i>XG3</i>	0.9281	0.9888	0.9926	0.9924	0.9924	0.5423	Matrix	80.281±2.48
<i>GC1</i>	0.8320	0.9912	0.9973	0.9973	0.9873	0.4965	Matrix	95.592±3.15
<i>GC2</i>	0.8761	0.9931	0.9987	0.9973	0.9802	0.5343	Matrix	86.761±3.22
<i>GC3</i>	0.9525	0.9923	0.9834	0.9937	0.9962	0.6335	Hixon Crowell	86.793±2.77
<i>XC1</i>	0.8555	0.9805	0.9946	0.9891	0.9538	0.5624	Matrix	76.914±2.56
<i>XC2</i>	0.8897	0.9915	0.9942	0.9889	0.9731	0.5803	Matrix	79.408±1.87
<i>XC3</i>	0.9484	0.9958	0.9862	0.9969	0.9894	0.6339	Hixon Crowell	72.992±1.65

gum (Al-Saidan et. al.2005). The formulation XG1 showed release of 92.67% in 12h. When Xanthan gum and Carrageenan gum were combined at different ratios a greater retarding effect was observed at all the ratios. Xanthan and Carrageenan gum swell rapidly from the beginning of the dissolution and form a viscous gel as shown in Figure 2. Hence a prolongation of drug release is seen in all the combinations of Xanthan and Carrageenan gum. The formulations XC1, XC2 and XC3 showed 76.75%, 79% and 72.99% release for the period of 12h. In the combination of Guar gum and Carrageenan gum as shown in Figure 2 it was seen that as the amount of Carrageenan gum in the matrix increases drug release is decreased. This may be due to the high initial water uptake and swelling of Carrageenan gum (Guptaa et.al. 2001). Among the different combinations GC1 showed highest drug release of 95.71% in 12h.

**ig; 2. Drug Release study of Ambroxol HCl Sustained Release Matrices of various combinations of gums.**



#### Stability Studies:

At the end of the testing period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content, and subjected to in vitro drug release studies.

No visible changes in the appearance of the matrix tablets were observed and a significant change was not seen in the drug content and drug release at the end of the storage period.

#### 4. DISCUSSION:

The presence of anionic side chains on the Xanthan gum molecules enhances hydration and makes Xanthan gum soluble in cold water. When Xanthan gum is used as the only retarding polymer, drug release follows a Matrix type model and hence it can be concluded that the passage of drug is through the hydrated layer (Phaechamud et. al. 2007). To analyse the release mechanism of the drug through the matrix, Peppas equation was

used (Korsmeyer et. al. 1983). In case of Xanthan gum the n value was 0.5571 i.e. Anomalous transport or Non-Fickian diffusion which suggested that the drug release occurs by swelling as well as erosion. In case of Guar gum, three processes namely water penetration, gelatinization and diffusion for release of drugs from guar gum matrices are reported (Ughini et.al. 2004). As guar gum is a hydrophilic colloid it dissolves and forms pores filled with liquid from which drug can diffuse. In the case of Guar gum matrices, when Guar gum is used as the only retarding polymer, First order model is concluded. Guar gum dissolves and forms pores filled with liquid from which drug can thereafter diffuse (Fukuda et. al. 2006). The drug release mechanism from Guar gum follows Fickian diffusion i.e. n value of 0.4423, which suggests that the drug release from the Guar gum matrices is by water penetration, gelatinization and diffusion. Carrageenan gum swells rapidly and increases the drug diffusion pathway and hence causes reduction in drug release. In case of Carrageenan matrices, Matrix type model is concluded which shows that the passage of drug is through the hydrated layer (Rosario et. al. 2002). The drug release mechanism from the Carrageenan matrices showed Anomalous behaviour i.e. Non-Fickian diffusion with n value of 0.5633 which shows that the drug is released by swelling as well as erosion in the latter part of the dissolution period.

In case of combination of Xanthan and Guar gum, as the amount of Xanthan gum in the matrix increases a greater retardation of drug is observed. This may be due to the greater degree of swelling of Xanthan gum. When the concentration of Guar gum in the matrix is increased a higher initial release as well as increased drug release for a period of 12h is observed. This is due to the low water uptake of Guar gum as compared to Xanthan gum (Al-Saidan et. al.2005). When Xanthan gum and Guar gum are combined together, the formulations with high concentrations of Xanthan gum XG 3 considering the erodibility of Xanthan gum, Hixon Crowell model may be concluded and the drug is released by erosion and diffusion within the matrix which is confirmed by the n value of 0.5420 which shows Non-Fickian diffusion. Decreasing the concentration of Xanthan gum XG1 shifts the drug release kinetic to Higuchi model and shows Fickian diffusion.

When Xanthan gum and Carrageenan gum were combined at different ratios a greater retarding effect was observed at all the ratios. Xanthan and Carrageenan gum swell rapidly from the beginning of the dissolution and form a viscous gel. The viscosity of the gel layer plays an important part in controlling the release of the drug. Hence a prolongation of drug release is seen in all the combinations of Xanthan and Carrageenan gum. In case of Xanthan and Carrageenan gum matrices, a Non-Fickian release mechanism is observed for all the formulations.

In the combination of Guar and Carrageenan gum it was seen that as the amount of Carrageenan gum in the matrix increases drug release is decreased. This may be due to the high initial water uptake and swelling of Carrageenan gum (Guptaa et.al. 2006). As the amount of Guar gum in the matrix increases drug release

increases. In case of Guar gum and Carrageenan gum matrices, as the concentration of Carrageenan gum in the matrix is increased considering the erodability of Carrageenan gum the drug release mechanism follows Non-Fickian mechanism.

## 5. CONCLUSION

The swellability and hence the drug retardation was highest from Xanthan gum matrices and low from Guar gum matrices amongst all the gums. The different combinations of natural gums sustained the release of drug effectively. Hydrophilic diluents and hydrophobic diluents can be effectively used in the modulation of drug release from natural gum matrices. These findings could thus be of importance in developing a suitable model for sustained drug release technology.

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