

Original Article

## CONTROLLED-RELEASE EFFERVESCENT FLOATING MATRIX TABLETS OF METFORMIN USING COMBINATION OF POLYMERS

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### ABSTRACT

**Objective:** It is always challenging to prepare the floating gastro retentive formulation of the high dose drug. The present research was aimed to prepare gastro retentive controlled release, matrix tablets of metformin, using the combination of different ionic, anionic and polyanionic polymers with HPMC.

**Methods:** Formulations were prepared using sodium alginate, pullulan, kappa carrageenan, xanthan gum, poloxamer 68 in combination with HPMC K15M. All matrix tablets were prepared by direct compression method and evaluated for swelling, floating adhesive period and drug release.

**Results:** All the tablets showed acceptable physicochemical properties. Statistical analyses of data revealed that tablets prepared using HPMC K15M and kappa carrageenan, formulation F2, is best in terms of showing excellent floating properties, extended adhesion periods and sustained drug release characteristics with similarity factor as 92 on comparison with the theoretical release of the drug.

**Conclusion:** The combination of HPMC K15M and kappa carrageenan can be further optimized by applying the appropriate statistical design.

**Keywords:** Metformin, Gastro retentive, HPMC K15M, Kappa carrageenan

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### INTRODUCTION

Metformin is an oral hypoglycemic agent, which belongs to the class of biguanide derivatives [1]. Metformin has an absolute bioavailability of 50-60 %, when administered orally due to its incomplete absorption, as it doesn't remain in the stomach for a longer period of time [2]. It has a biological half-life 1.5-1.6 h, and the main site of absorption for metformin is proximal small intestine of the GIT [3, 4]. Many approaches have been reported for increasing the bioavailability of metformin by preparing controlled release and gastro retentive dosage forms [5, 6].

The exhaustive literature research elucidates that several approaches have been tried for the preparation of gastro retentive metformin formulations. Stepensky *et al.*, 2001, established PK-PD rationale for the development of metformin CR formulations and it was concluded that GRDDS of this drug can be clinically advantageous [7]. Colo *et al.*, prepared pH-controlled peroral delivery of metformin and it was found that this mode of administration might allow the use of lower therapeutic doses of the drug compared to existing immediate or sustained-release products, thus minimizing side effects [8]. Ali *et al.*, (2007) prepared Hydro-dynamically balanced system for metformin as a single unit floating capsule, Gamma Scintigraphic studies revealed that the optimized HBS capsule was retained in the gastric region (stomach) for a prolonged period and pharmacokinetic studies showed an increase in AUC as compared to immediate release capsules of metformin [9]. Tack-Oon Oh. *et al.* (2013) prepared, highly Porous Gastro retentive metformin Tablets using a Sublimation method with 24 h floating time. Pharmacokinetic studies revealed that the mean plasma concentration of the GR tablets after oral administration was greater than the concentration of Glucophage XR [10]. Anita K. Laloo, *et al.* (2012) developed a controlled release formulation of metformin using swelling mechanism and compared it with gastro retentive marketed formulation, Glumetza®, of the same drug for understanding the relationship between the drug release rate, absorption rate and position in the gastrointestinal tract for GR and CR formulations. Diet was identified as the critical determinant of gastro retention in this research, as also reported in the clinic for Glumetza® and Proquin XRTM. Optimal gastric retention can hence be achieved by modulating the size/swelling rate of the dosage form together with the erosion rate [11].

An important factor for the development of gastro retentive dosage form is the selection of suitable hydrophilic polymer, which provides acceptable flotation characteristics and release of the drug substance. Drug dissolution from hydrophilic matrix systems is related to the entry of water into the matrices. Li *et al.*, (2008) suggested that many physicochemical phenomena occur simultaneously during dissolution [12]. The release mechanism of the drug from the polymeric matrix has been explained by many researchers, but in most of the studies, hydroxy propyl methyl cellulose (HPMC) is used as polymeric floating matrix system [13-15]. But the combination of HPMC with other ionic and anionic polymeric substances and their effect on the release of the drug has not been explored much. Dorozynski *et al.* (2011) used carrageenans and their mixtures with HPMC for preparing gastro retentive drug delivery systems of l-dopa. The formulations showed linear increase in the releasing rate constantly. In such formulations, carrageenans can modify the properties of polymeric matrices, to obtain tailor-made materials for drug delivery systems [16]. In another attempt, the effect of different viscosity grade HPMC polymers was checked on the Gastro retentive dosage form of metformin HCl [17].

This research has been conducted to check the combined effect of HPMC and other polymers on the release and gastro retentive properties of the formulation. The dose of metformin for a gastro retentive SR formulation was taken as 500 mg and was calculated in the same way as done by Mandal *et al.*, using the equation given by Rawlins with the available pharmacokinetic data given by Defang *et al.* (2005) [18-20]. The objective of the present research work was to prepare, characterize and evaluate floating, gastro retentive drug delivery systems of metformin using a combination of polymeric matrix, in order to achieve an extended retention of the drug in the upper GIT, which may result in enhanced absorption, improved bioavailability, decreased dosing frequency and increased patient compliance.

### MATERIALS AND METHODS

#### Materials

Metformin was obtained as a gift sample from Sanofi-Aventis Ltd., Ankleshwar. Sodium bicarbonate, sodium alginate and xanthan gum were procured from Sulab Reagents, Suvidhinath laboratories,

Baroda, HPMC K15M and carbopol 934 were procured from Astron Chemicals, Ahmedabad, poloxamer 68 Signet was purchased from Chemical Co. Pvt. Ltd., Mumbai, kappa-carrageenan was procured from Rajesh Chemicals, Vadodara. All other excipients were procured from the local market.

### Preliminary studies

From the literature review, it was found that HPMC is a good release retarding polymer and gives pH-dependent drug release. Hence, for weakly basic drugs, it gives increased release in acidic pH. As the dose of the drug is more so K15M grade was selected as release retarding polymer. For optimizing the quantity of HPMC K15M various batches of floating matrix tablet of metformin were prepared.

The amount of HPMC K15M was varied from 10% to 30% and the quantities of other additives were fixed (metformin 50%, sodium bicarbonate (NaHCO<sub>3</sub>) 18%, Magnesium stearate 1%). The weight of Microcrystalline cellulose was adjusted to keep the

total weight of the tablet as 1000 mg. Prepared formulations were evaluated for the floating lag time and total floating time.

### Formulation of metformin floating tablets

Tablets containing 500 mg of metformin were prepared, according to the design depicted in table 1, by direct compression technique. The respective powders, namely drug, release-retarding polymer(s) (HPMC K15M and sodium alginate/kappa-carrageenan/pullulan/xanthan gum/poloxamer 68/carbopol 934 P), a gas-forming agent, NaHCO<sub>3</sub>, were passed through sieve no. 20, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. microcrystalline cellulose and magnesium stearate were then added to the mixed powders. Mixing was continued for another 5 min. Finally, 1000 mg of each mixture were weighed and fed manually into the die of a rotary tablet compression machine (Cronimach Instrument, Ahmedabad, India), equipped with capsule shaped punch die set, to produce the desired tablets. The hardness of the tablets was adjusted at 5 kg/cm<sup>2</sup> using a Monsanto hardness tester (M. Shah and company, Vadodara, India).

**Table 1: It shows the composition (in percentage) of metformin HCl floating matrix tablets**

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Metformin	50	50	50	50	50	50
2	HPMC K15M	17	17	17	17	17	17
3	Sodium bicarbonate	18	18	18	18	18	18
4	Sodium Alginate	8	-	-	-	-	-
5	κ-Carrageenan	-	8	-	-	-	-
6	Pullulan	-	-	8	-	-	-
7	Xanthan gum	-	-	-	8	-	-
8	Poloxamer 68	-	-	-	-	8	-
9	MCC	6	6	6	6	6	14
10	Mg stearate	1	1	1	1	1	1

### Evaluation of prepared formulations

#### Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values±SD.

#### Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet 1000 mg was extracted in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined by UV spectroscopy (Shimadzu UV 1800 Double beam spectrometer, Shimadzu Corporation, Japan) at a wavelength of 230 nm after a suitable dilution with 0.1 N HCl.

#### Tablet friability

According to the IP specifications [21], 10 tablets were randomly selected from each batch and placed in the drum of a tablet friability test apparatus (DBK instruments, Electro quip Inst., Ahmedabad). The drum was adjusted to rotate 100 times in 4 min.

#### Tablet swelling ability

The swelling behavior of the tablets was determined, in triplicate, according to the method described by Dorozynski *et al.* [22]. Briefly, a tablet was weighed (W1) and placed in the petridish with 20 ml of HCl (0.1 N), maintained at 37±0.5 °C. After 8 h the tablets were removed from the petridish and the swollen tablet was then reweighed (W2) [23]. The swelling index (SI) was calculated using following formula.

$$\text{Swelling Index} = \frac{(W2 - W1)}{W1}$$

Where, W2 is the weight of the swollen tablets, and W1 is the initial weight of the tablets. The size of tablets, before and after swelling, was also measured.

#### In vitro buoyancy studies

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by

Rosa *et al.* [24]. Briefly, a tablet was placed in a glass beaker, containing 200 ml of 0.1 N HCl, maintained in a water bath at 37±0.5 °C. The floating lag time, "the time between tablet was placed in a glass beaker with HCl and its buoyancy" and total floating duration, "the time during which tablet remains buoyant", were recorded.

#### Tablet adhesion retention period

The adhesion retention period of the tablets was evaluated, in triplicate, by an *in vitro* method reported by Nakamura *et al.* (1996) for measuring the nasal mucoadhesion of some water-soluble polymers [25]. Briefly, an agar plate (2%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 0.1 N HCl and attached to the center of agar plate by applying a light force with a fingertip [26]. Five minutes later, the agar plate was attached to a USP disintegration test apparatus and moved up and down in 0.1 N HCl (pH 1.2) at 37±0.5 °C (fig. 1). The adhering tablet on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted visually.

#### Drug release studies

Drug release study of the prepared floating tablets was performed, in triplicate, in a USP Dissolution Tester Apparatus, type-II (Paddle method) (Electrolab TDT-08L, Purvi enterprise, Gujarat, India) at 37±0.5 °C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 ml of 0.1 N HCl solution (pH 1.2). Aliquots of 5 ml were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 230 nm, as mentioned before. At each time of withdrawal, 5 ml of fresh medium was replaced into the dissolution flask, to maintain the sink condition. The release of the prepared gastro retentive formulations was compared with the theoretical release of the drug by calculating similarity and dissimilarity factor [27, 28].

Similarity factor means the comparison of resemblance in the release pattern of two comparative formulations. Generally, a similarity factor in the range of 50-100 is acceptable according to the US FDA. It can be calculated using the following equation:

$$f2 = 50. \log\left\{1 + \frac{1}{n} \sum_{t=1}^n |R_t - T_t|^2\right\}^{-0.5} \times 100$$

Where, n is the number of dissolution sample times,  $R_t$  and  $T_t$  are the individual or the mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

Dissimilarity factor calculates the difference in percent dissolved between reference and test at various time intervals. It can be calculated using the following equation:

$$f1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \times 100$$

#### Drug excipient compatibility study

There is always the possibility of drug-polymer interaction in any formulation. The FTIR of pure drug and physical mixture of drug metformin Hydrochloride and polymers HPMC K15M and kappa carrageenan was performed using Fourier Transform Infrared Spectrophotometer (8400S DRS, Shimadzu Corp). The amount of drug and polymer of the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400  $\text{cm}^{-1}$ .

**Table 2: Results of the physical evaluation of prepared formulations**

Batch code	Weight uniformity	Hardness* ( $\text{kg}/\text{cm}^2$ )	Drug content* (%)	Friability* (%)
F1	Complies	5.7±0.95	100.74±0.94	0.25±0.09
F2	Complies	4.2±0.62	98.56±1.25	0.23±0.12
F3	Complies	4.0±0.28	98.73±1.37	0.13±0.10
F4	Complies	4.7±0.54	99.46±0.59	0.29±0.20
F5	Complies	4.6±0.65	100.98±0.94	0.44±0.16
F6	Complies	5.1±0.98	99.57±0.99	0.13±0.11

\*n=3, average of three determinations±SD

#### In vitro buoyancy studies

All the prepared formulations showed the floating lag time of fewer than 30 seconds, and tablets could float for more than 8 h, as shown in table no. 3. This indicates that a combination of polymers had no effect on lag time and total floating time of the prepared formulations, in this particular ratio.

#### Tablet swelling ability

The swelling index of formulation 2, with kappa carrageenan, was found to be highest Till 8 h, this formulation was intact and was deformed after 24 h, showing that the formulation would eventually go out of the stomach after the release of the drug, which is

## RESULTS AND DISCUSSION

### Preliminary studies

For optimizing the quantity of release retarding polymer, various batches of floating matrix tablet of metformin Formulations was prepared, using HPMC K15M by fixing the quantities of other additives. Results indicated that batches formulated with low polymer concentration got disintegrated in 0.1N HCl and the tablets prepared with the highest polymer concentration could not float.

It was found that HPMC K15M was giving satisfactory results from the concentration ranging 15-25%. The tablets prepared with 15% of HPMC could float for 3 h with 10 sec lag time. It was concluded that as the concentration of HPMC was increased, the floating lag time as well as floating time was also increasing. It was decided to take the minimum amount of HPMC K15M giving the satisfactory results, for further study to check the effect of the combination of other polymers with HPMC on gastro retention of tablets.

### Physical properties of floating tablet

The physical properties of the floating tablets were found to be satisfactory for all the batches. The hardness of all the batches was found to be in the range of 4-5.7  $\text{kg}/\text{cm}^2$ . Drug content of all the formulations was near 100% and friability was found to be within limits given in official books.

desirable. The minimum swelling index was calculated for the formulation with sodium alginate which means that the polymer doesn't promote water uptake by polymeric matrices containing HPMC. This formulation was intact even after 24 h, which suggests that formulation is not getting eroded eventually.

### Tablet adhesion retention period

The formulations gave the tablet retention between the range of 18 to 94 min. Tablets prepared with the HPMC K15M and kappa-carrageenan gave maximum adhesion retention of 93.50 min and formulation prepared using sodium alginate and HPMC K15M exhibited minimum adhesion retention period.

**Table 3: Results table for buoyancy, swelling ability and tablet retention period**

Formulation	Lag Time*(s)	Floating Time*(h)	Tablet adhesion retention period* (min.)	Swelling index (ratio)	Physical appearance of the tablet after swelling	
					8 h (width)	24 h
F1	15.25±1.20	>8	18.25±2.41	1.734	Intact 2 cm	intact
F2	10.71±2.36	>8	93.50±3.36	3.864	2.2 cm	deformed
F3	30.50±3.17	>8	66.41±3.42	2.755	1.8 cm	deformed
F4	12.07±1.70	>8	42.12±4.25	2.851	deformed	deformed
F5	15.65±2.20	>8	17.10±2.45	2.501	deformed	deformed
F6	30.75±4.96	>8	21.41±2.15	2.827	1.7 cm	deformed

\*n=3, average of three determinations±SD

#### Drug release studies

From this study, it was found that formulation F2 (formulation with HPMC K15M and kappa-carrageenan) was giving almost same release

pattern as that of a theoretical release pattern of the drug. Formulation F4 and F5 with xanthan gum and poloxamer 68, respectively, could not sustain the release of the drug for more than 6 h. After 2 h, 50% of the drug was released from these formulations. Hence, these polymers are

not the good release-retarding polymers for preparing matrix formulations. Formulations F1, F3 and F6 with sodium alginate, pullulan and only HPMC, respectively, showed the delayed release of

the drug from the matrix. Only 85% of the drug was released from these formulations in 8 h. All the formulations can be optimized by varying the concentration of the release retarding polymer.

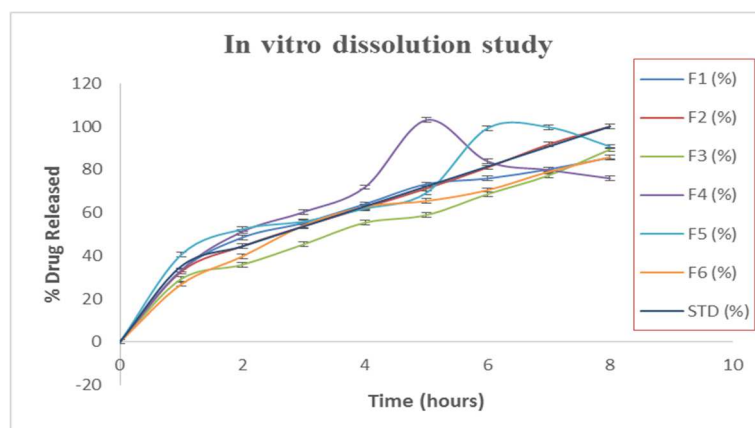


Fig. 1: It shows *in vitro* dissolution profiles of different floating tablet formulations in 0.1 N HCl\*, \*n=3, average of three determinations $\pm$ SD

The similarity and dissimilarity factor of the release data was calculated and formulation F2, with kappa carrageenan, gave f2 value as 92 and f1 value as 1. Formulation F3 and F4 doesn't pass the test as the values were out of the range. Other formulations i. e F1, F5 and F6 had the f2 value like 58, 53, 53 respectively.

#### Drug excipient compatibility study

The FTIR scan of the drug, polymers and physical mixture of drug and polymer was taken and the distinct peaks of metformin were present in the physical mixture of metformin and polymer, which proves that there was no interaction between drug and polymer.

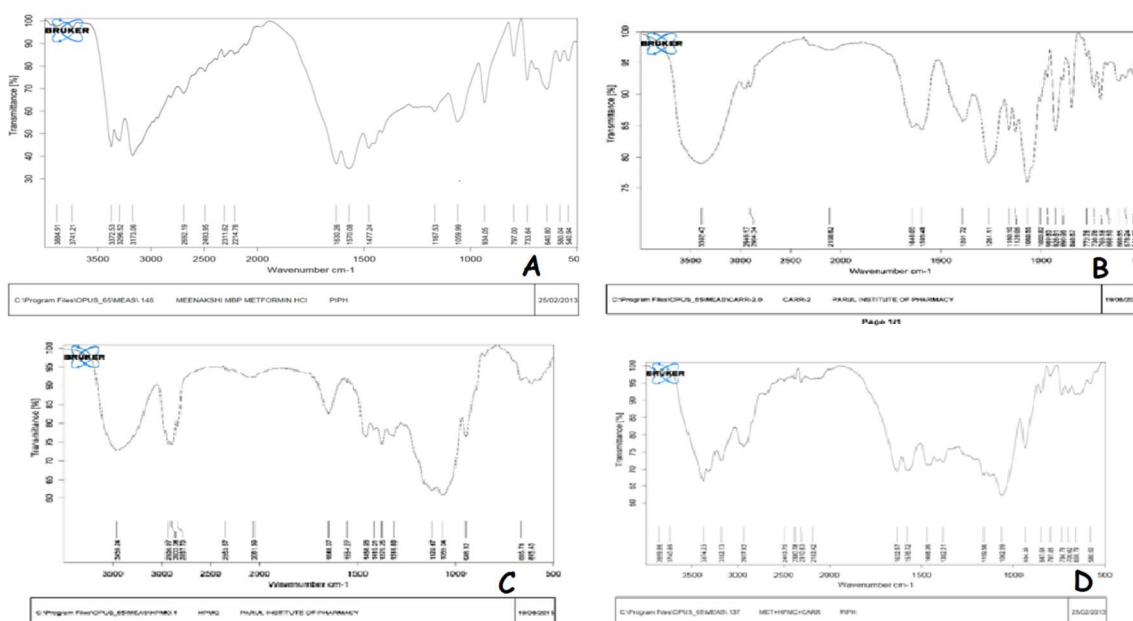


Fig. 2: FTIR scan obtained for metformin hydrochloride (A), kappa carrageenan (B), HPMC K15M (C) and optimized formulation (D)

#### DISCUSSION

The results of physical evaluation of the prepared dosage forms gave acceptable physical characteristics. The assay for drug content indicated acceptable content uniformity in the prepared tablets. Previous literature reported that viscosity of the gel-forming polymer influences the *in vitro* buoyancy [29]. All the formulations had floating lag time less than 31 seconds and floating time, more than 8 h, which means that variation of the polymers along with HPMC had no effect on the floating properties of the tablets. This shows that the flotation is dependent on the amount of sodium

bicarbonate present in the formulation. It has been reported earlier that strength of gel layer changes with the increase in polymer proportion which in turn will affect flotation of the tablet [30]. Hence, as the amount of sodium bicarbonate and HPMC was same for all the formulations, the floating properties were also similar.

The swelling index of formulation 2, with kappa carrageenan was found to be higher which proves the findings of Dorozynski *et al.*, (2011) where he showed that application of mixtures of carrageenan and HPMC, increase the swelling capacity of HBS formulations and suggested that this combination can be directly utilized as a starting

point in the development of various controlled release formulations [16]. The minimum swelling index was calculated for the formulation with sodium alginate which means that the polymer doesn't promote water uptake by polymeric matrices containing HPMC. This can be attributed to the pH-dependent solubility of sodium alginate as suggested by Timmins *et al.*, (1997), where it was proved that sodium alginate hydrates and swells in alkaline pH and doesn't form the gel layer in the stomach [31].

Agar plates were used to check the comparative adhesion retention of the prepared formulations as it is negative charges, same as that of mucin covering the mucous membrane [25]. Agar gel contains large numbers of negatively charged carboxyl and sulfate groups; therefore, they have a high negative charge. On performing the comparative adhesion retention period study for prepared tablets, it was found that formulation with kappa-carrageenan was retained on the agar plate for a longer period of time as compared to other formulations. As proved by Campo *et al.*, (2009), carrageenan is a high molecular weight sulfated polysaccharides and its high adhesion period may be due to hydrogen bonding or ionic interaction with agar [32]. Formulations prepared with poloxamer 68 and sodium alginate showed a minimum retention period as they have lower ability to interact with agar.

Tatavarti *et al.*, (2004), proved that incorporation of anionic polymers, in HPMC matrices is useful for developing a pH-independent release profile for weakly basic drugs [33]. The present study also revealed that incorporation of kappa-Carrageenan, a polyanionic polymer, in an HPMC matrix of metformin showed the best release pattern. This combination in F2 formulation showed an almost similar release pattern as that of a theoretical release pattern of the drug with maximum f2 value. Singh *et al.*, (2011) presented the release behavior of drugs from different natural polymers and gums [34]. They found that the presence of xanthan gum in the formulation can retard the release of the drug. Whereas, during the present study, formulation F4 prepared with xanthan gum could not sustain the release of the drug for more than 6 h. This may be because both the polymers and the drug used in the formulation are hydrophilic, which couldn't remain intact throughout the release study. Also, formulation F5 with poloxamer 68, could not sustain the release of the drug as the main requirement of floating drug delivery system is to form a cohesive gel barrier, with this polymer could not make [35]. Hence, both these polymers are not the good release-retarding polymers for preparing matrix formulations of the hydrophilic drug. Although, the change in the composition for both the polymers can be tried to get the desired release pattern of the drug. Formulation F6 prepared with only HPMC K15M showed delayed release of the drug, which is contradictory to the earlier findings where it was said that weakly basic drugs gives high release at lower pH when prepared with HPMC matrix alone [33,36]. The formulation prepared with HPMC and sodium alginate showed delayed release. This may be because of less hydration of sodium alginate and also because in acidic pH it doesn't contribute to the matrix erosion and hence the release of the drug [31]. Pullulan can be used for various coatings of the formulation [37]. In present research an attempt was made to check the ability of pullulan as release regarding polymer for floating formulation, but Formulations F3, with pullulan also showed delayed release of the drug which was almost same as that of formulation F6, this means that the presence of pullulan doesn't have much effect on the release pattern of metformin from the polymeric matrix system.

## CONCLUSION

Although, all the combinations tried above can be optimized by changing the amount of significant variables in the formulations. But the batches containing kappa-carrageenan polymer showed better release as compared to all other formulations. Moreover, the swelling index and adhesion retention of this formulation was better than all other formulations, which ensures the retention of the formulation in the stomach. Kappa carrageenan and sodium alginate, both are anionic polymers still the release pattern of the drug found to be different in both of them which indicates that the pH of the medium changes the properties of the polymer and hence the release of the drug. The basic mechanism of the gastro retention for

the formulation is floatation, but in the case of low level of fluid in the stomach, the mechanisms like mucoadhesion and swelling can retain the formulation at the required site, which can be better achieved by formulation with kappa-carrageenan. It has been already reported that the gastro restive formulations prepared by using the carrageenans can modify the properties of polymeric matrices, to obtain tailor-made materials for drug delivery systems. Hence, this combination of polymers can be further evaluated by applying appropriate design, to obtain the optimized gastro retentive formulation of metformin.

## CONFLICTS OF INTERESTS

Declared none

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