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Formulation development and *in-vitro* evaluation of gastroretentive drug delivery system of loxoprofen sodium: A natural excipients based approach

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Abstract: The limitations of conventional type delivery systems to retain drug (s) in the stomach has resulted in the development of novel gastroretentive drug delivery system. We developed single-layer effervescent floating tablets of loxoprofen sodium for prolong delivery in the stomach using natural polymers xanthan gum, guar gum and semisynthetic polymer HPMCK4M. All the formulations (F1-F9) were developed by varying concentrations of xanthan gum and HPMCK4M while guar gum concentration was kept constant. Two gas generating agent (s) incorporated were sodium bicarbonate and citric acid. All compendial pre and post-compression tests results were in the acceptable limits. FTIR analysis confirmed drug-polymer compatibility. The *in-vitro* drug release in simulated conditions i.e., 0.1 N HCl for 12 h revealed orderly increase in total floating time, i.e., less than 6 h for F1 over 12 h for F9. Formulations F1 to F4 were not capable to retard drug release up to 12 h, whereas F5-F7 for 12 h, while F8 and F9 for more than 12 h. Data fitting in various kinetic models showed that drug release best fit in first order kinetic model and F9 in zero order. Based on results data, F7 was the best among all.

Keywords: Guar gum, xanthan gum, HPMCK4M, loxoprofen, floating tablets.

INTRODUCTION

For the swift delivery of medication, oral administration is still believed to be most promising route due to the flexibility in its preparation, patient acceptance as well as ease of its administration (Ullah *et al*., 2015). Majority of conventional drug delivery systems intended for immediate release of drug(s) possess a number of complications, like multiple dosing for drugs with shorter half-life, which leads to variation in plasma drug concentrations. This may leads to unsafe practice for drug(s) having narrow therapeutic index (Tripathi *et al*., 2019). In addition, this needless variation in plasma drug concentration could lead to medication errors, which might results in rise or fall in the steady state concentration (Css) values beyond the effective therapeutic range. Furthermore, it is impractical for the immediate release drug to be absorbed beyond its absorption window in the gastro intestinal tract (GIT) (Tripathi *et al*., 2019, Mandal *et al*., 2016).

In a decade or two, several innovative drug delivery methods have modernized the medication with additional benefits. These new approaches actually reduce drug dosing rate, but still preserve therapeutic blood intensities for extensive time period. Moreover, these novel adopted techniques carry the active pharmaceutical ingredient to the target organ thus minimizing possible side effects. However, the absorption of drug is often insufficient due to physiological constraints like inconstant gastrointestinal transit, due to varying gastric emptying thus causing unpredictable absorption profiles with limited drug release so gastro-retentive drug delivery system (GRDDS) is an alternate to tackle this problem (Mukherjee *et al*., 2019).

Through GRDDS approach, the dosage form will persist in the gastric area for extended time period, extending the gastric residence time of drug(s) with ultimate absorption/bioavailability improvement and decreases drug wastage. Besides, it is also appropriate for delivering drug locally to the stomach and small intestine (Katta *et al*., 2018). The key adopted GRDD approaches comprises of floating, sinking, swelling, effervescence, muco-adhesive and magnetic type. In floating types (lower-density systems) system, the GRDD bulk density is kept low than that of the GI fluid that let the system to float in the stomach for an extended time period that permit drug release at the desired amount (Tripathi *et al*., 2019, Rossi *et al*., 2016). Based on its buoyancy, these systems may be non-effervescent floating (API mixed with gel-forming polymer) and effervescent floating type that utilizes

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effervescent agent (s) blended with hydrophilic polymers. Due to presence of effervescent agent the later type system when contact with GI fluid, liberates CO_2 due to chemical reaction. This CO_2 gas is trapped in the hydrocolloid matrix and gives the tablet buoyancy that considerably affects the drug release profiles. While hydrophilic polymers controls the drug release rate (Manjunath *et al*., 2017).

Though a range of synthetic polymers have been tried as release retardants in design of effervescent floating systems but utilizing natural polymers to extend the drug (s) delivery is field of dynamic research even though the dawn of synthetic biodegradable polymers. The natural excipients offers advantages of being inert, are somewhat inexpensive, produced from living organisms, nontoxic, easily biodegrade in the body and have ease of availability. As reported three well-known hydrocolloids (gel-forming agents) xanthan gum, guar gum and HPMC swells considerably on contact with GI fluids and sustains shape and bulk density below the gastric content (Kaushik *et al*., 2015). The use of these two polysaccharides as release retardants in both non-effervescent / effervescent floating type systems individually as well as blended with synthetic polymers has been well documented (Dey *et al*., 2014, Boorlagadda *et al*., 2014).

Loxoprofen sodium (LPS) is a non-sterodal anti-inflammatory drug (NSAID) in the propionic acid derived group, indicated for pain and inflammation related to musculoskeletal and joint disorders. Daily recommended dose of LPS is 2-3 tablets (Venkatesan *et al*., 2011). The objective of the present study was to design and optimize the single-layer effervescent floating tablets of LPS by direct compression method utilizing natural polymers.

MATERIALS AND METHODS

Materials

LPS was gifted by Selmore Pharmaceuticals Pakistan. All excipients used in studies like guar gum, HPMCK4M and xanthan gum were purchased from local market. Excipients like PVP and sodium bicarbonate were kind gifts from Obson Pharmaceutical Pakistan and talc, citric acid, lactose and magnesium stearate were bought from Merck, Germany. All the reagents like hydrochloric acid, ethanol and methanol purchased from Merck, Germany. All these chemicals and reagents were of analytical grades and used as such without additional processing.

Preparation of single-layer effervescent floating tablets

Direct compression method was used to prepare floating tablets of LPS. In final formulation two natural polymers (guar gum and xanthan gum) and one semisynthetic polymer (HPMCK4M) were used as release retardants. Gas generating agent (s) selected were sodium bicarbonate ($NaHCO_3$) and citric acid (CA). Polyvinyl pyrolidone (PVP) was added as binder whereas talc and magnesium stearate (Mgst) were incorporated as lubricants and glidants and lactose was introduced as diluent. All the materials were weighed precisely and sieved (sieve #40). All excipients excluding lubricant and glidant were mixed for 15 min in mortar and pestle. This was followed by the addition of lubricant and glidant to the powder blend and again mixed for 5 min. After mixing, the powder was compressed into tablet using single punch machine. Experimental tablets final formulations are given in table 1.

Pre-compression powder evaluation studies

The analysis of LPS was done by HPLC consuming SS column (15 cm x 4.6 mm) as per our previous reported method (Zaman *et al*., 2015). To determine the LPS equilibrium solubility in water, ethanol, 0.1N HCl and methanol 20 mg of drug was put in 50 mL stoppered bottle (n=3), that were shaken automatically at 37°C±0.5°C for 24 h, all other steps followed as per adopted standard procedure and at the end drug concentration determined by UV-spectrophotometer at 295 nm against a constructed calibration curve (R^2 0.9993). The melting point of LPS was estimated by melting point apparatus. The flow characters of granules were assessed by their estimation of angle of repose, bulk and tapped density, compressibility index (Carr's index) and Hausner's ratio using documented official methods (Shi *et al*., 2011).

Drug polymer compatibility studies

The FT-IR spectrophotometer (Shimadzu, UK) was used to study spectra of LPS, individual polymer and their blend in final optimized formulation by KBr disc method. The scan set ranged 4000 - 400 cm^{-1}.

Post-compression studies

Final tablets formulations physical features like hardness (Monsanto hardness tester, Curio, Pakistan), thickness (Vernier caliper, Trickle Brand China), weight variation (performed on 20 tablets), friability (100 revolutions / 4 min, Friabilator, Curio Pakistan), and content uniformity test performed on randomly selected 20 tablets. All these tests executed as per documented methods.

In-vitro buoyancy studies

The buoyancy test was estimated by reported floating lag time method (Jiménez-Castellanos *et al*., 1994). Tablets taken in 100 mL beaker having 0.1N HCl and calculation of time taken by a tablet to rise and float (surface) was noted (Chinthala *et al*., 2012).

Swelling index (SI)

Floating tablets water gain was estimated by putting tablet in Petri-dish having 50 mL of 0.1N HCl and individual tablets swelling of every single formulation was studied for 1-6 h. After stated time intervals individual tablet

taken and surplus water removed and were again weighed. The SI was determined by using standard formula (Chinthala *et al*., 2012).

In-vitro dissolution studies

Floating tablets drug release rate was assessed using USP type II apparatus (paddle method). The medium used was 900 mL of 0.1N HCl at 37 ± 0.5°C temperature at 50 rpm. After 60 min 5 mL sample taken and fresh medium added to maintain sink conditions, withdrawn solution than filtered through 0.45µ membrane, diluted to appropriate concentration with 0.1N HCl and absorbance measured at 295 nm using a UV/Visible spectrophotometer (PG instrument T80 England) estimated against constructed calibration curve in 0.1N HCl (2 µg/mL – 10 µg/mL).

Analysis of in-vitro drug release

The obtained *in-vitro* release data than fitted to a number of kinetic models, such as zero-order (Costa and Lobo, 2001), first order (Gibaldi and Feldman, 1967), Higuchi's model (Higuchi, 1963) and Korsmeyer-Peppas model, also known as power law (Peppas, 1985).

$Qt = Q_o + K_o t$ (1)

$\log C = \log Co – K_t / 2.303$ (2)

$Q = k t^{1/2}$ (3)

$Q = KH t^{1/2}$ or $M_t / M_0 = kt ½$ (4)

Where, M_t = amount of un-dissolved drug at time (t), M_o = amount of un-dissolved drug at time (t) = 0, t = time of sampling, K_o is the zero and K_1 is the first-order release rate constant, Qt = un-dissolved drug quantity at time (t), KH is the Higuchi's release rate constant.

STATISTICAL ANALYSIS

The results of the three independent experimental samples obtained were averaged and then presented as mean ± SD. The analysis was performed with the available version of Design-Expert (7.1.6) software (Stat-Ease Inc. USA).

RESULTS

Pre-compression powder evaluation studies

LPS showed solubility in water, ethanol, 0.1N HCl and methanol. The MP 202-206 ºC also confirmed its purity. The powder blends angle of repose calculated ranged between 25.36°±0.2 to 27.34°±0.3. These values range revealed remarkable flow properties of powder blends. Hausner's ratio values ranged between 1.11±0.01 to 1.18±0.02 that is in 'good' range of USP criterion (Hausner, 1967, Shi *et al*., 2011)**.** The percentage of CI was determined by Carr's compressibility index. The Carr's index ranged 11.35±0.01%–14.91±0.03% for all formulations (F1–F9) that also fell in 'good' criterion of USP in terms of powder flow (Carr, 1965)

Drug Polymer Compatibility studies

Drug-polymers compatibility studies were executed by FTIR spectrophotometer using KBr disc method. Initially individual IR spectrum of API and all excipients were obtained. Similarly to check compatibility of drug with added polymers and other excipients, FTIR of final formulations were also obtained (fig. 1).

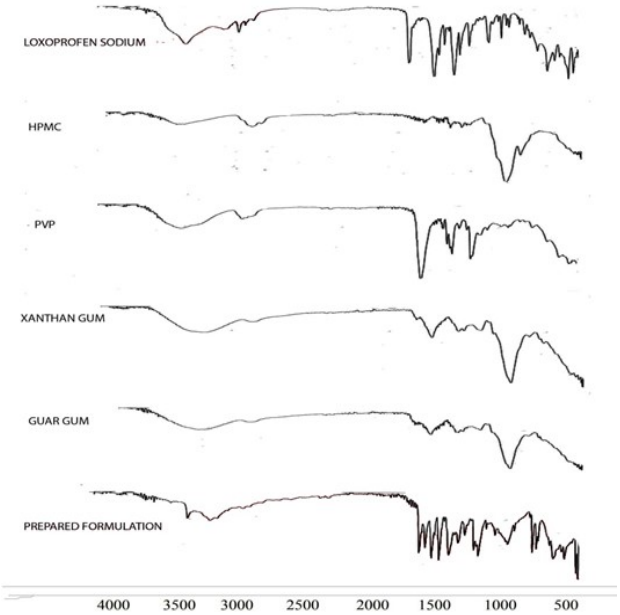

Fig. 1: FTIR spectra of the obtained formulations showing characteristics peaks.

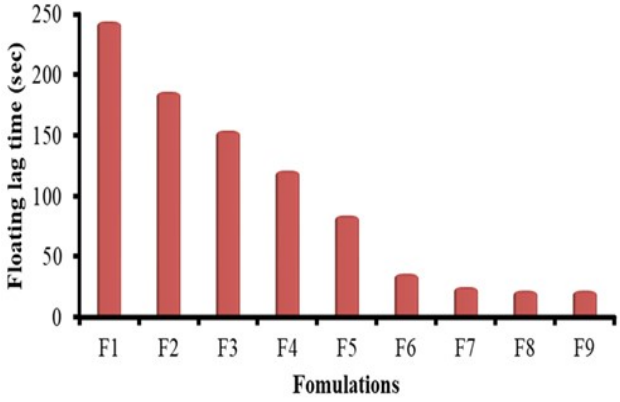

Fig. 2: *In-vitro* buoyancy studies for the formulations during experiments.

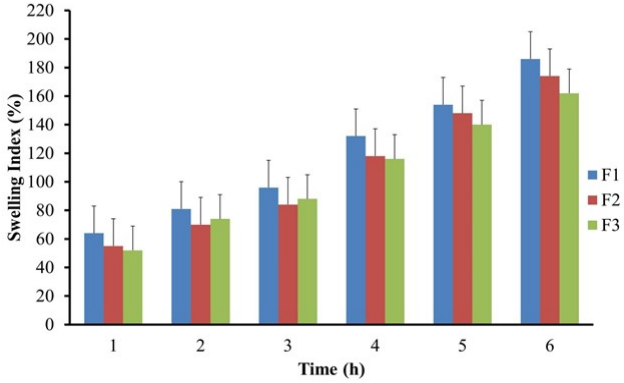

Fig. 3: Swelling index for the matrix system (F1–F3) at various intervals.

Table 1: Composition of single-layer floating tablets of loxoprofen sodium (F1-F9).

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loxoprofen Sodium	60	60	60	60	60	60	60	60	60
Guar Gum	55	55	55	55	55	55	55	55	55
Xanthan gum	165	165	137.5	110	100	82.5	65	65	51.25
HPMCK4M	27.5	55	82.5	110	137.5	165	192.5	206.25	220
PVP	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5
Sodium bicarbonate	82.5	82.5	82.5	82.5	82.5	82.5	82.5	82.5	82.5
Citric Acid	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5
Magnesium Stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Lactose	105	77.5	77.5	77.5	60	50	40	26.25	26.5

Table 2: Results of various test performed for the matrix (F1-F9) post-compression.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diameter (mm)	11.9 ±0.01	11.88 ±0.02	11.89 ±0.01	11.9± 0.03	11.9± 0.03	11.8 ±0.01	11.9± 0.02	11.8 ±0.01	11.9 ±0.01
Thickness (mm)	4.4 ±0.04	4.2 ±0.01	4.4± 0.02	4.4± 0.02	4.2± 0.01	4.3± 0.01	4.2± 0.01	4.3 ±0.02	4.4 ±0.02
Hardness (kg/cm^2)	7.2 ±0.01	9.6 ±0.01	8.4± 0.01	7.6± 0.00	8.1± 0.00	7.4± 0.01	8.7± 0.03	7.3 ±0.02	7.2 ±0.01
Friability (%)	0.24 ±0.01	0.21 ±0.03	0.20± 0.03	0.28± 0.01	0.36± 0.04	0.30± 0.01	0.41± 0.02	0.32 ±0.01	0.29 ±0.02
Assay (%)	98.21 ±0.02	99.92 ±0.01	100.1± 0.03	98.8± 0.00	99.96 ±0.01	98.71± 0.02	100.4± 0.02	99.24 ±0.02	98.42 ±0.01
Weight variation (mg)	552.2 ±0.30	549.9 ±0.43	552.6± 0.39	555.2± 0.45	549.9 ±0.41	550.9± 0.39	549.8± 0.41	551.6 ±0.32	549.8 ±0.41
Content Uniformity (%)	98.7 ±0.10	98.94 ±0.14	99.6± 0.11	99.1± 0.01	99.4 ±0.13	98.5± 0.13	99.8 ±0.12	99.1 ±0.10	98.7 ±0.10

Table 3: Swelling index (%) of the prepared tablets (F1–F9) at various time intervals.

Formulation	Time (h)					
	1	2	3	4	5	6
F1	64	81	96	132	154	186
F2	55	70	84	118	148	174
F3	52	74	88	116	140	162
F4	48	69	92	108	121	158
F5	45	62	89	101	122	146
F6	39	41	64	87	98	136
F7	31	46	69	89	97	84
F8	32	46	72	88	91	106
F9	24	40	66	79	84	96

Table 4: Drug release profile from the prepared formulations at different time intervals applied with various kinetic models.

Kinetic model		Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	R^2	0.5373	0.7152	0.7500	0.8062	0.8208	0.9183	0.9596	0.9565	0.9743
	k_0	11.184	10.705	10.608	10.414	9.799	9.134	8.581	8.095	7.398
1st order	R^2	0.9848	0.9846	0.9818	0.9765	0.9809	0.9747	0.9609	0.9736	0.9722
	k_1	0.354	0.287	0.274	0.252	0.221	0.179	0.154	0.140	0.118
Higuchi	R^2	0.9414	0.9672	0.9650	0.9605	0.9585	0.9413	0.9135	0.9159	0.8845
	k_H	33.308	31.452	31.060	30.298	28.454	26.134	24.287	22.932	20.758
Korsmeyer peppas	R^2	0.9067	0.9434	0.9441	0.9494	0.9504	0.9731	0.9789	0.9788	0.9793
	k_{KP}	38.616	31.001	29.209	26.141	23.963	17.644	13.579	13.061	10.003
	n	0.424	0.507	0.531	0.575	0.587	0.697	0.789	0.780	0.862

Post-compression studies

The diameter of all tablets in F1-F9 ranged 11.8±0.001 mm to 11.9±0.002 mm and the thickness ranged between 4.2±0.01mm and 4.4±0.02 mm respectively. These values were in the standard limits. All the compressed tablets of LPS displayed good mechanical strength in term of hardness that ranged between 7.20±0.00 kg/cm^2 and 9.60±0.01 kg/cm^2. Friability values calculated were also in acceptable range of 0.21% to 0.41%. Average weight was observed between 549.8±0.41 to 555.2±0.45 and thus passed pharmacopeia 7.5% limit. Content uniformity test of LPS floating tablets were between 98.5±0.13 to 99.8±0.12, which meet specified pharmacopeia limits. Summary of various test performed for the matrix tablets post compression are given in table 2.

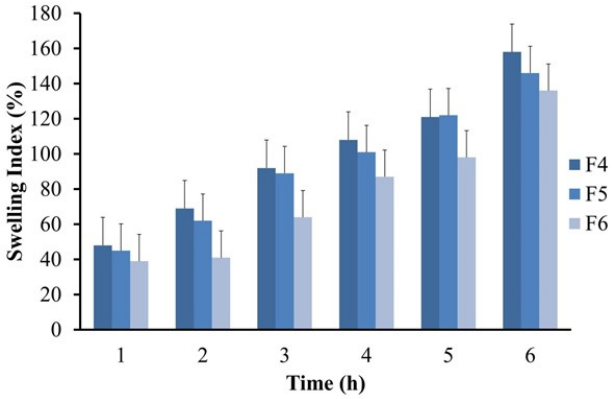

Fig. 4: Graphic representation of the swelling index at various time intervals for formulations F4–F6.

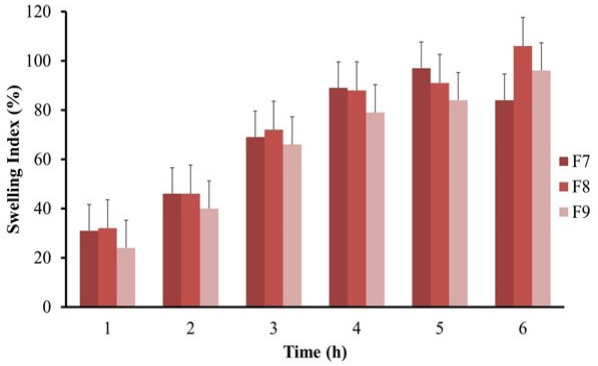

Fig. 5: Swelling index for the formulations F7–F9 containing higher concentration of HPMC at different time intervals.

In-vitro buoyancy studies

The calculated FLT for formulations F1, F2 & F3 were 244±3, 186±2 and 154±3 and TFT values were <6 h for F1 and were found to be > 6 h for both F2 & F3. This is due to the higher concentration of HPMCK4M in formulations F2 & F3 i.e. double in F2 than F1 and almost 3 times in F3 to F1 formulation. For formulations F4, F5 and F6, FLT values were 121±3, 84±4 and 136±2, while TLT values were < 9 h for F4 & F5 but were > 9 h for F6. The formulations F7, F8 and F9 FLT values were 25±1, 22±1 and 24±2 and TFT were over 12 h for all formulations containing maximum concentrations of HPMCK4M (fig. 2).

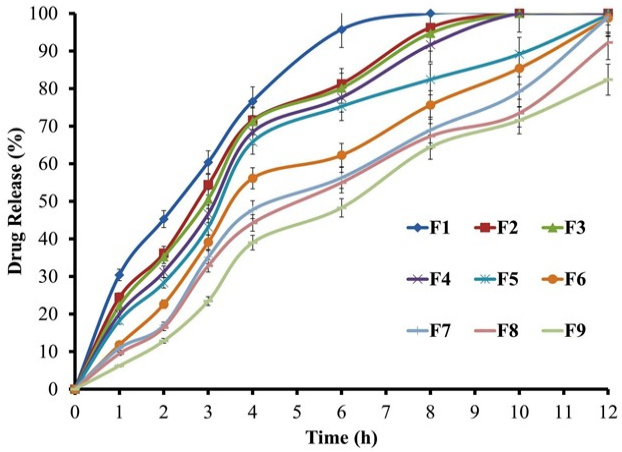

Fig. 6: *In-vitro* drug release of formulations (F1-F9) using simulated gastric conditions (0.1 N HCl).

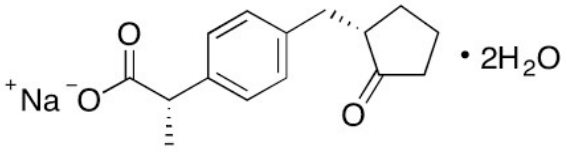

Fig. 7: Structure of Loxoprofen sodium Dihydrate

Swelling index (SI)

The swelling index loxoprofen sodium tablets studied up to 6 h. The swelling index ranged from lowest 96% in F9 formulation to highest 186% in F1 (figs. 3-5 and table 3).

In-vitro dissolution studies

In-vitro drug release in dissolution studies were observed for almost twelve hours at specified time intervals. Very interesting results were observed, after 1 h 30% drug was released from F1 that decreased with increased concentration of HPMCK4M to 22%. F1 was capable of retaining the drug release for 6 h, F2 for 8 h and F3 for around 9 h. Formulation F4 released almost 50% of drug in first 3 h while remaining 50% released in next 7 h, so this formulation retarded release for 10 h. Three formulations F5-F7 released complete drug in 12 h, while 50% release of drug was varied in all of them, F8 formulation released only 92% drug in 12 h and F9 formulation released only 82% of drug. FLT and TFT values of F7 formulation as described were 25±1 & More than 12 h, as TFT for F6 & F5 were around 9 h (fig. 6).

DISCUSSION

The average assay determined by HPLC ranged 98.21%±0.02 and 100.4% ±0.02 respectively. The powder all pre-compression studies illustrated acceptable physical features for all experimental formulations under study (F1-F9) as described in detail above. The combinations of

LPS and added polymers i.e., Guar gum, Xanthan gum and HPMCK4M were examined by IR spectroscopy using KBr disc method. These characteristic stretching bands studies after pre-formulation study, revealed no chemical interactions (fig. 1). FTIR spectra of pure LPS presented a noticeable peak at 1730 cm^{-1} attributable to the carboxylic group, and asymmetric C–H band (CH_3 and CH_2) of the aromatic ring showed stretching at 2350 cm^{-1} and 2930 cm^{-1}, correspondingly. The peaks at 1140 cm^{-1} and 1400 cm^{-1} were attributed to C–H bending and CH_2 scissoring (Pineda *et al*., 2004). As shown in fig. 1, FTIR spectrum for final formulation was also obtained. The LPS typical peak (1730 cm^{-1}) because of carbonyl stretch of the carboxyl part is marginally moved to 1740 cm^{-1} in final formulations with polymers. Similar outcomes have been reported for LPS in polymeric film coated pellets (Khalid *et al*., 2018). Similarly all post-compression tests performed on tablets were in acceptable range (s) as per official compendial criteria.

The *in-vitro* buoyancy studies data in simulated gastric conditions (0.1 N HCl, pH 1.2), showed variations in buoyancy for all tested formulations (fig. 2). As effervescent base (sodium bicarbonate) generated CO_2 gas due to reaction with HCl in dissolution medium. The CO_2 generated got trapped in the gel (made by HPMCK4M hydration), thus decreased the tablets density. As the density fell below 1 (density of water), the tablets became buoyant. The floating lag time (FLT) as well as total floating time (TFT) values were obtained by dipping the LPS tablets in 0.1N HCl in a 100 mL beaker. FLT is the actual time taken by a tablet to reach surface top and thus start floating. The concentration of guar gum remained constant in all formulations, and the xanthan gum concentration decreased from 165 mg to 51.25 mg per tablet from F1 to F9 and the concentration of HPMCK4M increased from 27.5 to 220 mg per tablet in vice versa. These values confirmed direct relation of polymer type and concentration to that of total floating period in formulated tablets. It has been noted that the increase in polymer concentration enhanced the TFT.

The results of tablets SI revealed direct relationship of swelling with the extension of time and the concentration of xanthan gum (fig. 3). In contrast, formulations that contained higher proportion of HPMCK4M gave low swelling indices (Fig. 4 and 5). The proposed reason may be hydrophilicity of the polymer. Polymers clustered round the tablets and formed a puffy gel boundary that actually controlled drug release from matrix tablets. Similar swelling patterns have been reported for atenolol floating tablets where xanthan gum had higher welling indices to that of HPMCK100M and HPMCK4M (Havaldar *et al*, 2008).

The percent total drug release vs time for F1-F9 is given in fig. 6. The influence of polymers types and its concentrations on the drug release pattern was keenly observed. The weight of tablets in each formulation was set at 550 mg. In all experimental formulations the quantities of guar gum (10%), sodium bicarbonate (15%), PVP (5%), citric acid (3%), talc (1%) and Mgst (1%) remained constant, while concentration of xanthan gum and HPMCK4M varied (Table 1). In F1 & F2 the %age of gum was 30% and 25% in F3, while HPMCK4M was 5 & 10% in F1 & F2 while it increased to 15% in F3. In F4 formulation the concentration of both these polymers was 20%. From F5 to F9 the concentration of xanthan gum further decreased (18.1 to 9.3% systemically) and HPMCK4M concentration increased (25 to 40%).

Drug release data from the prepared formulations was tested by various kinetic models (Table 4). The results of the drug release from formulations F1-F8 follow first order kinetic model, whereas F9 follows zero order. In order to get best fit model, 60% of the drug release data was put in Korsmeyer-Peppas model (Ullah *et al*, 2015). The calculations of "n" values of all the formulations revealed that the drug release pattern was non-Fickian ($0.45 \leq n \leq 0.89$). This indicated that the drug release from all the formulations as carried out by both diffusion and erosion of polymer matrix.

CONCLUSION

The use of natural polymers markedly affects the *in-vitro* overall performance of LPS tablets. Incremental variations in concentration of polymers led to efficient selection of polymers concentrations for the development of effervescent floating tablet formulations. All nine formulations gave satisfactory physical performance. All experimental formulations *in-vitro* performance showed drug retardation capabilities owing to gel formation and achieve buoyancy due to gas generating agents. Still, among all formulation F7 may be regarded the best based on its overall performance and may possibly be appropriate candidate for additional clinical testing. These outcomes suggest that effective development of GRDDS is possible, by careful selection of the type and concentration of natural polymers.

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