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FORMULATION, DEVELOPMENT AND EVALUATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM OF RISPERIDONE

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ABSTRACT

Aim and Objective: The study aimed to manufacture Bucco-adhesive tablets of Risperidone and characterize the effectiveness of the drug by incorporating it into the mucoadhesive drug delivery system. The sustained release tablets reduced the dose frequency by increasing residence time. **Methods:** For this study, five tablet formulations were synthesized by the wet granulation technique. Polymers like Carbopol, HPMC, CMC, Chitosan, and Xanthan gum, with varying concentrations, were used in each formulation. The effectiveness of the mucoadhesive tablets was ascertained by performing various tests like analysis of physicochemical parameters like friability, hardness, content uniformity, weight variation, and swelling studies. The DSC and FTIR analysis gave validation about the compatibility between drug and excipients. Furthermore, in vitro release analysis and stability studies were performed that suggested good bio-adhesive strength of prepared tablets. **Results:** All formulations showed good results for the physical characterization tests, post-formulation tests, and stability and compatibility studies, but Fs had shown the optimum results in in vitro release studies and stability. solver software was used, and different models were applied to in-vitro release data. Kinetic modeling studies showed that these formulations followed Korsmeyer-Peppas mode of release, with Fs showing non-Fickian release. Stability studies showed not more than 5to10% change in the drug concentration which indicated the stability of formulations. No incompatibilities of polymer and drugs were proved by the results of DSC and FTIR. **Conclusion:** Conclusively, the results demonstrated that optimum mucoadhesive tablets of risperidone will be proved as a promising delivery system with reduced dosing frequency for the treatment of psychotic disorders.

Keywords: Buccoadhesive tablets, Risperidone, Kinetic studies, Sustained release, Mucoadhesion.

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INTRODUCTION

Risperidone, a serotonin and dopamine antagonist, is an antipsychotic drug that has proved to make a significant improvement in the treatment of schizophrenia **[1, 2]**. It is available as an oral solution, intramuscular injection, and a conventional tablet. It belongs to BCS class II category whose absorption is dependent on dissolution **[3]**. Risperidone shows extensive first-pass metabolism via the oral route. Patient adherence to oral treatment can be a challenge for bipolar and schizophrenic disorders posing the frequency of oral tablets as a big issue. Long-term intramuscular injection of risperidone gives relief from these concerns to a certain extent. However, a non-invasive delivery system is needed to be developed that can solve all of the presenting issues and challenges **[4]**. The buccal route is advantageous over the conventional oral route due to many reasons. Drugs absorbed through this route bypass the pre-systemic metabolism and GI route. The buccal mucosa has a rich blood supply and the blood drains directly into the jugular vein, so the buccal dosage form can be applied easily and can be discarded in emergency or undesirable effect. Buccal drug delivery systems can be formulated for systemic and local drug delivery in different dosage forms i.e., tablets, patches, gels, discs, and films. The mucoadhesive DDS has gained popularity owing to its efficiency over conventional dosage forms **[5]**. It avoids rapid flushing of drugs from the gastrointestinal mucosa. It substantially improves the drug transit time [**6**]. The mucin molecules interact with mucosal tissue and that's how the residence time of the drug at its application site and thus bioavailability of the drug is increased **[7]**. The mucoadhesive drug delivery system has become increasingly adopted due to its efficient drug delivery

in case of buccal, ocular, vaginal or local GIT their residence time of the drug by sticking them in the mucosal layer. Drugs can be targe to systemically to the CNS using the mucosal drug delivery strategy **[9**]. Example given is the risperidone mucoadhesive formulation. The present study aims to design and optimize a sustained controlled Bucco adhesive tablet formulation of risperidone reducing dosage frequency to one tablet one day, solving most of the presenting issues with the risperidone drug delivery, giving systemic effect to CNS, and improving schizophrenia and bipolar disorder management remarkably.

MATERIALS AND METHODS

Materials

Risperidone, Carbopol, chitosan, HPMC, CMC, Mannitol, Lactose, Xanthum gum, isopropyl alcohol magnesium stearate and talc, were bought from Sigma Aldrich. Distilled water was used a as solvent. Each 250 mg tablet has an active ingredient, i.e., risperidone, along with some polymers, lubricants, and preservatives.

Methods of Preparation

We designed five different types of Bucco adhesive formulations employing the same wet granulation method with varying quantities as shown in Table 1. Each 250mg buccoadhesive tablet, containing risperidone 2mg was prepared by using the non-aqueous wet granulation method using isopropyl alcohol, with PVP in it. All the ingredients including risperidone were added in ascending order of weight and then mixed in pestle and mortar. The granulation was performed using the IPA+PVP mixture. A damp mass was formed which was then passed through sieve no. 10. It was passed through sieve no. 16 after drying. Lubricants such as talc, and magnesium stearate were added at end the and these were mixed in a polyethylene pouch, the tablets were then compressed by station rotary compression machine. These tablets were then evaluated by following tests.

PRE-FORMULATION STUDIES

The flow properties of risperidone were determined before compressing the tablets. Density, Hausner ratio (HR), and Carr's index (CI), were calculated from obtained powder using equations. The inverted funnel method was employed to find out the angle of repose of the pure drug. And the angle of repose was used as calculated from the formula. The melting point of pure drug was calculated using Fisher John's apparatus.

Solubility

The solubility of risperidone was checked in phosphate buffer 6.8, Octanol, and methanol. Log P value was calculated by using the Octanol-Phosphate buffer 6.8 system to determine the lipophilicity or hydrophilicity of the substance.

diseases **[8]**. Mucoadhesive dosage forms increases

POST FORMULATION

The compressed tablets were evaluated for hardness, weight variation, and friability. The hardness test was performed on twenty randomly selected tablets a using digital hardness tester. Weight variations on10 tablets [**10**] and calculated by following formula:

%Weigh variation = (Initial Weight-Actual weight/ Actual weight)*100.

Friability studies were performed by using Curio Friability apparatus on twenty tablets. The apparatus was set on 50 rpm for 4 minutes. After the completion, tablets were reweighed for friability percentage calculation.

Determination of Drug Content Test

10 Tablets were crushed in the pestle and mortar and 30mg of the powder was weighed. Then powder was dissolved in the 30ml solution of 6.8 pH phosphate buffer. And the sample was centrifuged for 30 min on the 80-1-centrifuge machine at 50 rpm speed. 1 ml from the supernatant solution diluted with 9 ml of the 6.8 pH phosphate buffer. The sample was run on the CECIL 7000 series spectrophotometer for absorbance studies [**11**].

Swelling Index

To evaluate the swelling index, the initial weight of the formulation was calculated (w1). Then tablets were added in 15ml phosphate buffer of 6.8 pH in a petri-dish, then placed in an incubator at 37 degrees. The sample were taken from it during the intervals of 0.5, 1, 2, 3, 4, 5, 6 and 7 hr. Final weight (w2) was determined and swelling index was determined by following formula [**12**].

$$\text{Swelling Index} = 100(w_2-w_1)/w_1$$

Dissolution Studies of Risperidone

In vitro drug release from risperidone tablets was performed in USP dissolution apparatus II at 100 rpm. The study was carried out in 450 ml phosphate buffer 6.8 at 37±0.5 ºC. The samples wing taken out for 24 hours. The 1 ml samples were further diluted to the tenth part and observed under spectrophotometer.

COMPATIBILITY AND STABILITY STUDIES

Fourier Transform Infrared (FT-IR) Spectroscopy Analysis

Heston Fourier Transformer Infrared Spectrophotometer was used for this test. FT-IR analysis was used to find out interaction between the risperidone, polymers, and excipients. To find out this, IR spectra for tablets, drug, and polymers were determined in the range of 264 – 276 cm^{-1} with the cm^{-1} resolution by FT-IR spectrophotometer [**13**] and results are obtained in the form of graph.

Table 1: Composition of buccal tablets of risperidone.

Composition(mg)	F_N	F_S	F_J	F_F	F_M
Carbopol	142.8	-	50	95.42	95.6
Chitosan	95.6	-	-	-	142.8
HPMC(K100)	-	109.84	-	-	-
CMC	-	24.9	93.5	-	-
Mannitol	-	24.9	-	-	-
Lactose	-	59.9	93.5	54.1	-
Xanthan gum	-	-	-	95.42	-
Magnesium stearate	4.85	2.60	1.25	1.29	4.85
Talc	6.88	2.60	1.25	1.29	6.88

Table 2: Flow properties tests of the bucco adhesive risperidone tablets.

Bulk density	Tapped density	Compressibility Index	Hausner ratio	Angle of repose
0.541	0.641	16.12	1.19	24

Table 3: Solubility analysis of risperidone.

Solvent	**Solubility**
Methanol	1mg/ml
Octanol	0.5mg/ml
Phosphate buffer 6.8	0.1mg/ml

Table 4: Weight variation, hardness, friability tests, and contents uniformity.

Sr No.	**Weight of tablets (mg)**	**Contents uniformity %**	**Hardness (kg/cm^2)**	**Friability test %**
F_N	248	-0.77%	8.5	0.97%
F_S	275	1.16%	8.3	0.69%
F_J	240	-4.69%	8.7	0.76%
F	260	-1.16%	8.8	0.98%
F_M	274	6.2%	8.9	0.77%

Differential Scanning Calorimetry (DSC) Analysis

A differential scanning calorimeter (DSC 4000; PerkinElmer, Waltham, MA, USA) was used. 5 mg of sample was placed in aluminum pan. It was heated from 100 ^oC to 280 ^oC. The rate of heating was 20 ^oC/min under 30ml/min N_2 flow. Using Pris v eleven software, the peaks of the onset of melting point were determined in the form of thermograms.

Stability Studies

The tablets were subjected to accelerated stability studies for one month and temperature of 40 ± 5 degrees and relative humidity of 75 ±% maintained. The sample were taken, on 10^{th}, 20^{th} and 30^{th} day for assay and tested for drug uniformity [**14**].

RESULTS AND DISCUSSIONS

By the work plan, mucoadhesive tablets prepared by using the wet granulation method were evaluated for their physical characteristics, content uniformity, in-vitro release, swelling index, FTIR analysis, DSC analysis, and stability studies.

The results of the angle of repose conducted on the granules suggested good flow properties of risperidone as its value is less than 30. Carr's compressibility index and Hausner ratio results demonstrated the good packing quality of the granules as indicated in **Table 2** [**15**]

The melting point obtained was 170.13 ^0C. Which is the exact melting point of risperidone, showing that the material was pure. The drug is soluble in phosphate buffer of 6.8 pH [**16**], as shown in Table 3. It shows that the drug is slightly acidic [**17**].

The solvents for partition co-efficient were octanol and phosphate buffer of 6.8 pH. The drug was more soluble in the organic layer (octanol) and the log P value obtained was 3.59. This proves the lipophilic nature of risperidone [**2**]. The weight variation of all formulations suggested that there was uniformity in the weight of the tablets, as no

two tablets showed ±5% weight variation and no tablet showed ±10% variation [**18**], as shown in **Table 4**. While the hardness of the tablets was in the acceptable range of 4-10 kg/cm^2 depicted the tablets can withstand the rigor during packaging and shipping [**19**]. And friability was less than 1 %, which shows good mechanical strength [**20**].

Content Uniformity

All formulations were tested for content uniformity to ensure the uniform amount of drug in the tablets. The sample is taken randomly from the powdered tablets and a test was performed on these samples. All formulations showed satisfactory results, as shown in **Table 5**.

Swelling Index

Peak swelling index values were shown by the formulations containing both Carbopol and Chitosan (F_N, F_M). Hydration led to swelling which led to adhesion. This mechanism was responsible for the bioadhesive behavior of the tablets [**21, 22**]. Figure 3 shows final the form of the tablet after swelling studies.

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Table 5: Swelling index and content uniformity of all formulations.

Formulations	Content Uniformity	Swelling Index
F_N	89%	4.23 ± 0.041
F_S	95%	2.30 ± 0.013
F_J	92%	3.36 ± 0.017
F	85%	3.78 ± 0.089
F_M	91%	4.65 ± 0.061

Figure 1: Tablets after swelling studies.

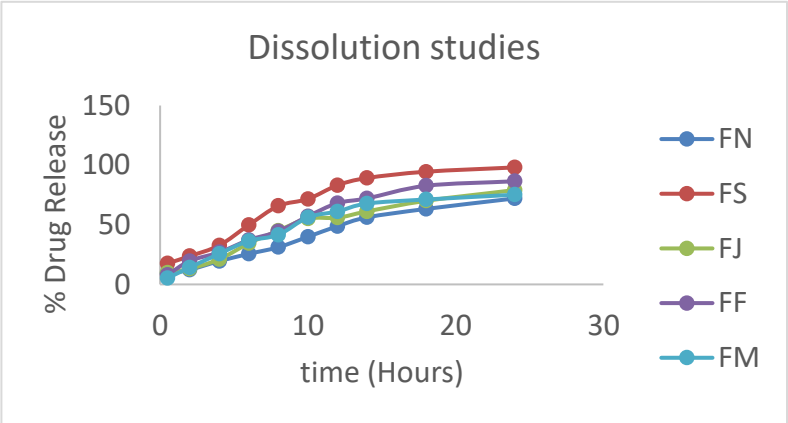

Figure 2: Dissolution studies of risperidone.

Dissolution Studies

In vitro dissolution studies are performed for 24 hours for each formulation [**23, 24**]. All formulations showed % drug release above 70%, with maximum rea lease of 98.1% by F_S., as shown in **Table 6**. Throughout the interval, the tablets successfully maintained their physical integrity. **Figure 2** shows the collective dissolution curve of all formulations.

Kinetic Studies

The dissolution data for each formulation was subjected to different models to determine the mode of drug release. Correlation coefficient (R^2) values were obtained for zero order, first order, Higuchi and Korsmeyer-Peppas model [**1**]. Among formulations, F_N, F_S, and F_M followed Korsmeyer-Peppa first-order order kinetics, which means that the drugs showed dissolution-controlled rate as well as anomalous release. The n value ($0.45<n>0.89$), as shown in **Table 7**, suggested a non-Fickian release. The process of dissolution is dominant over diffusion as evident by the first order model [**25**].

The formulation F_J and F_F followed zero order and Korsmeyer-Peppas with Fickian release ($n<0.45$), meaning they followed concentration-independent kinetics. The release in these formulations occurred through diffusion and erosion of the polymeric matrix. Since the maximum. release till twenty-four hours was shown by F_S, and it was decided as the optimum formulation.

FTIR Spectroscopy

As depicted in **Figure 3**, the spectrum of risperidone showed an aromatic characteristic peak of C-H band stretched at 3,058 cm^{-1}, sharp N-O band at 1,533 cm^{-1}, strong C=O band at 1,644 cm^{-1}, C-N band at 1,350 of oxazole ring, C-F band stretched 1,1350 cm^{-1} and a weak band of tertiary amine C-N at 1,192 cm^{-1} of the piperidine ring. The spectrum of CP gives abroad stretched peak of -OH of carboxylic acid at 3,400–2,800 cm^{-1}. C=O stretching of the carbonyl group at 1,699 cm^{-1}, and C-OH asymmetric band at 1,166 cm^{-1}.

Bucco-adhesive tablets displayed the characteristic peaks of all important groups of Risperidone and Carbopol. The decrease in carbonyl group intensities was also evidence which could be due to the formation of the hydrogen bond. The presence of all characteristic peaks in FTIR analysis ruled out the possibility of incompatibility between lactose, Carbopol, and risperidone in Bucco-adhesive tablets [**24, 26**].

Table 6: Dissolution studies for each formulation.

Time	F_N	F_S	F_J	F_F	F_M
0	8.91	17.6	9.92	8.06	5.3
2	12.3	23.7	13.12	19.6	14.2
4	19.5	32.7	21.1	26.9	25.7
6	25.6	49.8	34.4	37.2	36.5
8	31.2	65.8	45.1	44.5	41.6
10	39.9	71.6	55.2	57.1	56.2
12	48.8	83.1	55.9	68.13	61.2
14	56.2	89.2	61.2	72.1	67.8
18	63.3	94.5	70.1	82.7	71.2
24	72.1	98.1	79.1	86.5	75.2

Table 7: Kinetic release studies.

Sr. no	Zero Order			First Order			Higuchi			Korsmeyer-Peppas			
	R^2	AIC	MIC	R^2	AIC	MIC	R^2	AIC	MSC	R^2	AIC	MSC	Slope value
F_N	0.88	43.2	3.68	0.97	55.2	4.89	0.908	44.7	1.07	0.95	65.3	2.10	0.62
F_S	0.10	19.1	1.29	0.97	59.0	6.21	0.884	31.2	1.25	0.92	53.6	2.49	0.49
F_J	0.97	56.3	4.59	0.31	47.1	3.41	0.930	39.2	2.91	0.98	61.2	1.09	0.37
F	0.99	61.5	5.23	0.96	41.2	2.09	0.83	47.1	2.46	0.96	52.9	3.67	0.23
F_M	0.11	51.9	5.78	0.98	50.4	7.19	0.89	23.7	3.10	0.97	55.2	5.08	0.04

DSC Analysis

The characteristic sharp peaks of the ingredients showed the purity and state of the materials. If pure risperidone is used as a standard, the changes detected in DSC thermograms will prove chemical incompatibilities. The endothermic peak of Risperidone, as shown in **Figure 4** has a melting point onset at 173.32 ˚C and a peak is obtained at 177.21 ˚C. DSC analysis of buccal tablets displayed specific peaks of all ingredients. The melting point of the formulation was increased because of the presence of polymers.

The DSC profile was consistent with the FTIR spectrum and proved that no chemical incompatibilities (degradation, oxidation, and hydrolysis) and solid-state incompatibilities (solubilization, polymorphism, crystallization) in the drug and polymers existed. Weak physical interactions are developed which changes the result slightly but, causes no major issues [**27-29**]

Stability Studies

The data obtained from the stability studies, as depicted in **table 8**, showed that the tablets were stable as no tablet showed a change in an initial assay for more than 5-10 % [**14, 30**].

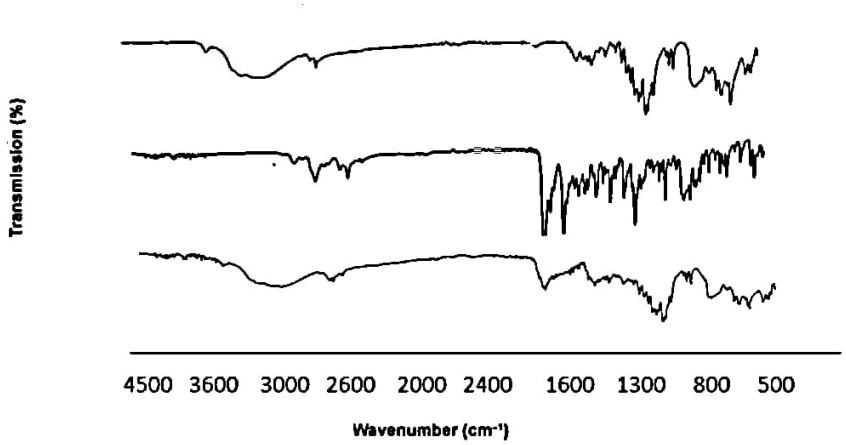

Figure 3: FTIR of active drug, polymer and bucco-adhesive risperidone tablets.

Table 7: Stabilities studies of risperidone formulations.

Formulation	**Stability test (%)**			
	Day 10	**Day 20**	**Day 25**	**Day 30**
F_N	72.1%	70.2%	69.1%	67.3%
F_S	98.1%	96.5%	95.1%	94.3%
F_J	79.1%	77.8%	76.1%	73.6%
F	86.5%	84.1%	83.0%	82.7%
F_M	75.2%	74.1%	72.0%	70.9%

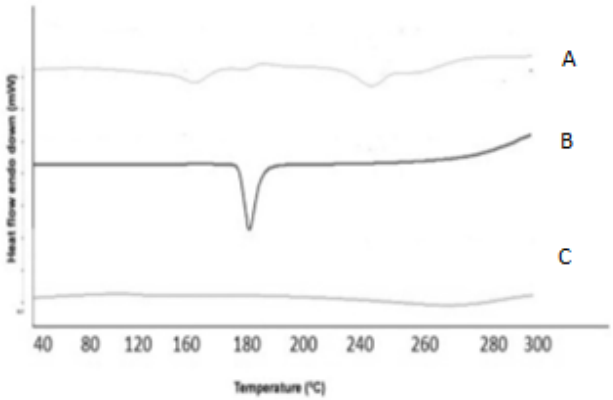

Figure 4: DSC analysis of risperidone and its formulation (A - risperidone, B- tablet and C- polymer).

CONCLUSION

From this study, the following inferences can be drawn. The optimum sustained-controlled release of Bucco-adhesive tablets of risperidone (F_S) can be prepared by using non-aqueous wet granulation with isopropyl alcohol using polymers like HPMC and CMC, along with PVP and mannitol. We aimed to design a formulation that offered minimum dosing frequency. This tablet successfully met the criteria. This optimum Bucco-adhesive tablet of risperidone offers a viable alternate pathway for systemic delivery by bypassing the first effect, for the treatment of diseases like schizophrenia, bipolar, and other psychotic disorders. But further studies are needed to determine the pharmacokinetic characteristics, safety profile, side effects, and performance of drug in vivo.

REFERENCES

1. Çelik B. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug design, development and therapy. 11, 3355, 2017.
2. Chopko TC, Lindsley CW. Classics in chemical neuroscience: risperidone. ACS chemical neuroscience. 9 (7), 1520-1529, 2018.
3. Khames A. Investigation of the effect of solubility increase at the main absorption site on bioavailability of BCS class II drug (risperidone) using liquisolid technique. Drug delivery. 24 (1), 328-338, 2017.
4. Chue P. Risperidone long-acting injection. 2016.
5. Jin BZ, Dong XQ, Xu X, Zhang FH. Development and in vitro evaluation of mucoadhesive patches of methotrexate for targeted delivery in oral cancer. Oncology letters. 15 (2), 2541-2549, 2018.
6. Tang C, Guan Y-X, Yao S-J, Zhu Z-Q. Preparation of ibuprofen-loaded chitosan films for oral mucosal drug delivery using supercritical solution impregnation. International journal of pharmaceutics. 473 (1-2), 434-441, 2014.
7. M. Ways TM, Lau WM, Khutoryanskiy VV. Chitosan and its derivatives for application in mucoadhesive drug delivery systems. Polymers. 10 (3), 267, 2018.
8. Silva MM, Calado R, Marto J, Bettencourt A, Almeida AJ, Gonçalves LM. Chitosan nanoparticles as a mucoadhesive drug delivery system for ocular administration. Marine drugs. 15 (12), 370, 2017.
9. Sosnik A, Das Neves J, Sarmento B. Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: A review. Progress in Polymer Science. 39 (12), 2030-2075, 2014.
10. Akgeyik E, Kaynak M, Çelebier M, Altinoz S, Şahin S. Evaluation of pharmaceutical quality of conventional dosage forms containing paracetamol and caffeine available in the Turkish drug market. Dissolution Technologies. 23 (2), 2016.
11. Zaid AN, Al-Ramahi RJ, Ghoush AA, Qaddumi A, Zaaror YA. Weight and content uniformity of lorazepam half-tablets: A study of correlation of a low drug content product. Saudi Pharmaceutical Journal. 21 (1), 71-75, 2013.
12. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, Pandey J, Parajuli-Baral K. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 7 (3), e06439, 2021.
13. Lin S-Y, Wang S-L. Advances in simultaneous DSC–FTIR microspectroscopy for rapid solid-state chemical stability studies: Some dipeptide drugs as examples. Advanced Drug Delivery Reviews. 64 (5), 461-478, 2012.
14. Ahuja S, Scypinski S: Handbook of modern pharmaceutical analysis: Academic press; 2010.
15. Lunkad SH, Sarode S. Formulation and Evaluation of Mucoadhesive Tablet of Valsartan. Asian Journal of Pharmaceutical Research. 9 (4), 229-237, 2019.
16. Mealey D, Svärd M, Rasmuson ÅC. Thermodynamics of risperidone and solubility in pure organic solvents. Fluid Phase Equilibria. 375, 73-79, 2014.
17. Kumar BP, Kavitha P, Devi KJ. Formulation design and evaluation of mucoadhesive buccal tablets of nitroglycerin. International Journal of Pharmacy and Pharmaceutical Sciences. 6 (7), 251-259, 2014.
18. Katori N, Aoyagi N, Kojima S. The Study of the Applicability of Content Uniformity and Weight Variation Test—The State of Commercial Tablets and Capsules in Japan—. Chemical and pharmaceutical bulletin. 49 (11), 1412-1419, 2001.
19. Mccoy CF, Millar BG, Murphy DJ, Blanda W, Hansraj B, Devlin B, Malcolm RK, Boyd P. Mechanical testing methods for drug-releasing vaginal rings. International Journal of Pharmaceutics. 559, 182-191, 2019.
20. Upadhyay NK, Gupta RK. Formulation and In-vitro evaluation of mucoadhesive tablet of famotidine.
21. Umarji B, Patil R, Birajdar R, Mysore S, Bilagi S, Audurti D. Formulation and in vitro evaluation of mucoadhesive buccal tablets of furosemide. World J Pharm Pharm Sci. 1 (3), 1041-1063, 2012.
22. Arora G, Malik K, Singh I, Arora S, Rana V. Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using Salvia plebeian gum. Journal of advanced pharmaceutical technology & research. 2 (3), 163, 2011.
23. Vantimita SR, Jeganath S. Formulation and Evaluation of Gastroretentive Drug Delivery System of Eprosartanmesylate.
24. Mylangam CK, Beeravelli S, Medikonda J, Pidaparthi JS, Kolapalli VRM. Badam gum: a natural polymer in mucoadhesive drug delivery. Design, optimization, and biopharmaceutical evaluation of badam gum-based metoprolol succinate buccoadhesive tablets. Drug delivery. 23 (1), 195-206, 2016.
25. Bakr F, Soliman M, Elsabbagh H. Formulation and In-Vitro, Ex-Vivo, and In-Vivo Evaluation of Mucoadhesive Buccal Tablets Containing Labetalol Hydrochloride for Enhancement of Systemic Bioavailability. Journal of Advanced Pharmacy Research. 6 (1), 15-27, 2022.
26. Rukmangathen R, Yallamalli IM, Yalavarthi PR. Formulation and biopharmaceutical evaluation of risperidone-loaded chitosan nanoparticles for intranasal delivery. Drug Development and Industrial Pharmacy. 45 (8), 1342-1350, 2019.
27. Yan X, Wang S, Sun K. Long-acting risperidone dual control system: preparation, characterization and evaluation in vitro and in vivo. Pharmaceutics. 13 (8), 1210, 2021.
28. Wen J, Arthur K, Chemmalil L, Muzammil S, Gabrielson J, Jiang Y. Applications of Differential Scanning Calorimetry for Thermal Stability Analysis of Proteins: Qualification of DSC. Journal of Pharmaceutical Sciences. 101 (3), 955-964, 2012.
29. Rashad AA, Nageeb El-Helaly S, Abd El Rehim RT, El-Gazayerly ON. Chronological Delivery of Antihypertensive Drugs in Bilayered Core-in-Cup Buccoadhesive Tablets: In Vitro and In Vivo Evaluation. AAPS PharmSciTech. 21 (1), 21, 2019.
30. Narayan S, Choudhary M. A review on stability studies of pharmaceutical products. Int Jr of Appl Pharm & Bio Res. 2 (3), 67-75, 2017.