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FORMULATION AND EVALUATION OF MICROSPHERES BASED ORO DISPERSIBLE TABLETS OF ROXITHROMYCIN

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ABSTRACT

Objective: The objective of the present work is to mask the intensely bitter taste of Roxithromycin and to formulate an oro dispersible tablet (ODT) of the taste-masked drug by incorporation of microspheres in the tablets. **Method:** Microspheres of Roxithromycin were prepared by solvent evaporation method using acetone as solvent for pH-sensitive polymer: Eudragit EPO and light liquid paraffin act as the encapsulating medium. The physical properties of prepared microspheres were evaluated with regard to yield, drug content, flow properties, particle size, in vitro drug release and taste. The average size of microspheres was found to be satisfactory in terms of the size and size distribution. The ODTs prepared by direct compression method and evaluated for hardness, thickness, weight variation, friability, disintegration time, drug content, wetting time, in vitro disintegration, in vitro drug release and stability. **Result and discussion:** Comparison of the dissolution profiles of microspheres in different pH media showed that microspheres having drug: polymer ratio of 1:3 to 1:5 produced a retarding effect in simulated salivary fluid (pH 6.8) and sufficient flow properties was shown in the drug: polymer ratio of 1: 3 compared to other ratios. So these microspheres were further used for formulation of ODTs using different concentration of superdisintegrants. ODTs containing Croscarmellose sodium 4.8% showed batter drug release profile as compared to other Superdisintegrants. **Conclusion:** Effective taste-masking was achieved for Roxithromycin by of preparation of microspheres and ODTs of acceptable characteristics.

Keywords: Taste Masking, Roxithromycin, Microspheres, Oro Dispersible Tablets, superdisintegrants.

INTRODUCTION

Roxithromycin is one of the macrolide antibiotics for respiratory infections. It is very bitter in taste, hence present study was carried out to enhance dissolution properties of Roxithromycin.[1] Regarding patient compliance, taste of oral formulations is very important especially in pediatric patients . In recent decades, new dosage forms have been formulated by a variety of pharmaceutical researches. Most of these efforts have been focused on ease of medication. Among the dosage forms developed to facilitate ease of medication, the orally dissolving tablets (ODTs), which are the most widely, used commercial products.

ODTs offer advantages of administration without water, ease of swallowing, rapid onset of action and convenience of dosing. When an ODT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.[2] the two parameters that need to be considered in the development of ODTs are taste masking of bitter drug and the disintegration time. Various taste-masking technologies have been extensively reviewed. Solvent evaporation is a relatively simple and convenient method for the preparation of taste-masked microspheres.

The drug particles are surrounded by a polymer which prevent leaching of the drug into the saliva but allow the release of the drug in the stomach.[3] Therefore, the purpose of the present study was to develop a fast disintegrating tablet of Roxithromycin by direct compression and to mask the bitter taste of Roxithromycin. Such tablet should disintegrate rapidly in the saliva without need of water and release the drug instantly for immediate therapeutic effect, and be of acceptable taste.[4]

MATERIALS AND METHODS

Materials

Roxithromycin was obtained as a gift sample from Intas pharmaceutical Private Limited, Eudragit EPO was gifted by Evonick, Mumbai. Croscarmellose sodium, Crospovidone, Sodium starch glycolate was procured from Oxford laboratory, Mumbai. Light liquid paraffin, Acetone was procured from Chemdyes Corporation, Ahmadabad. Manitol was procured from Oxford laboratory, Micro crystalline cellulose (MCC) was procured from Astron chemicals, Mumbai. All other chemicals used were of analytical grade and used without further purification.

METHODS

Preparation of taste masking microspheres by solvent evaporation method

Eudragit EPO was dissolved in acetone on a magnetic stirrer to obtain uniform mixing. Roxithromycin was then added to the above solution. To this mixture, magnesium stearate was added5%w/v. The polymer drug solution so obtained was injected into light liquid paraffin at a low stirring speed (200–600 rpm) of mechanical stirrer for about 3 h until all the acetone evaporated. N-Hexane/petroleum ether was added to the system for hardening of the microspheres. Microspheres were separated by following filtration through a Whatman filter paper. Microspheres were then washed with n-hexane and the washed microspheres were dried in an oven maintained at 37°C for 24 h. Dried microspheres were stored at room temperature. Various drug: polymer ratios were selected for the formulation of microspheres. The formulation parameters and process parameters for different batches of microspheres were evaluated.[3]

Table 1 Formulation of microspheres

Ingredients	M1	M2	M3	M4	M5
Roxithromycin	1.50g	1.50g	1.50g	1.50g	1.50g
Eudragit EPO	1.50g	3.00g	4.50g	6.00g	7.50g
Light Liquid Paraffin	400 ml	400 ml	400 ml	400 ml	400 ml
Acetone	20 ml	20 ml	20 ml	20 ml	20 ml
Petroleum ether	150 ml	150 ml	150 ml	150 ml	150 ml

Evaluation of Microspheres

Fourier Transform Infrared Spectroscopy (FTIR)

The drug, polymer and drug polymer complex were subjected to IR spectroscopy to check the drug polymer Interaction using FT-IR (SHIMADZU 8400 S) and the KBr disk method.

Flow properties

The prepared microspheres were evaluated for bulk density, tapped density, angle of repose, carr's index and hausner ratio.

Percentage yield determination[9]

The prepared microspheres were completely dried in an oven maintained at 37°C for 24 h and then weighed. The percentage yield was calculated by the following formula:

$$\% \text{ Yield} = \frac{\text{Weight of microspheres} \times 100}{\text{Total weight of solid material}}$$

Entrapment efficiency

The entrapment efficiency was calculated by the formula:

$$EE = \frac{\text{Practical drug content} \times 100}{\text{Theoretical drug content}}$$

Entrapment efficiency was calculated by digesting outer layer of 20 mg microspheres in 100 ml 0.1 N HCl was added. The solution was then warmed for a few minutes, filtered n& 1 ml of filtrate was made up to 10 ml with 0.1 N HCl. The solution was analyzed using UV spectrophotometer at 203 nm to determine amount of Roxithromycin entrapped in microspheres. The calculations were made in triplicate. [9, 10]

Particle Size determination

Size distribution and average particle size of microspheres was calculated with optical microscopy. Optical microscope was fitted with eye piece micrometer which was then calibrated with a stage micrometer. Size of about 100 microspheres was calculated from each batch and then the average size was calculated. [10]

In-vitro taste evaluation of microspheres

Microspheres equivalent to 50 mg Roxithromycin were placed in volumetric flask with 25ml of pH 6.8 phosphate buffer (simulated saliva) and were stirred for 5 min. the resulting mixture was filtered and analysed using UV-Visible spectrophotometer at 203 nm. [11]

Preparation of Oro Dispersible Tablet

Microspheres formula (M3) that gave the best physical property and taste masking results was selected for preparation of ODTs by direct compression technique. MCC was used as directly compressible diluent. Mannitol was used as filler and also to impart cooling sensation in mouth. Crospovidone, Croscarmellose sodium and Sodium starch glycolate were used as superdisintegrants in tablet weight. The microspheres equivalent to 50 mg drug, and superdisintegrants were accurately weighed and mixed. Thereafter, the mannitol was accurately weighed, added. Finally the amount of magnesium stearate was mixed. Then the powder mixture was directly compressed using 10 mm punch. [12]

Table 2 Formulation of ODTs

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
Roxithromycin equivalent to 50mg	126	126	126	126	126	126	126	126	126
Crospovidone (mg)	6	8	10	-	-	-	-	-	-
Croscarmellose Sodium (mg)	-	-	-	6	8	10	-	-	-
Sodium Starch Glycolate (mg)	-	-	-	-	-	-	6	8	10
Micro Crystalline Cellulose (mg)	39.5	37.5	35.5	39.5	37.5	35.5	39.5	37.5	35.5
Mannitol (mg)	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2

Evaluation of Oro Dispersible Tablet

Weight variation[13, 14]

Twenty randomly selected tablets were weighed individually and all together. The average weight and the percentage deviation were calculated. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percentage deviation was calculated using the following formula:

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{Average weight} * 100}{\text{Average weight}}$$

Friability test

The friability of 20 tablets was measured using a Roche Friabilator. 20 preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines, and the percentage of weight loss was calculated.[13]

Hardness test

The hardness of six tablets was determined by using a Monsanto tester and the average values were calculated.[14]

Dimensions

The dimensions (diameter and thickness) of six tablets were determined to within ± 0.01 mm by using vernier calipers and the average values were calculated.[13]

Disintegration Time

Disintegration of tablets was performed using disintegration tester. A minimum of 6 tablets of each product were tested. One tablet of each product was placed in each of the six tubes of the basket. Then the apparatus was operated using phosphate buffer pH 6.8 maintained at 37±2°C as a disintegration medium.[14]

Wetting time

The wetting time of the tablets was measured by using a simple procedure. Five circular tissue papers of 6 cm diameter were placed in a glass petridish. Ten ml of water was poured on the tissue papers. A tablet was carefully placed on the top surface of the tissue paper. The time required for water to reach the center of upper of the tablet was noted as wetting time.[15]

Dissolution

In-vitro Dissolution studies were performed using USP Type II dissolution paddle apparatus. The dissolution test was performed using 900 ml of 0.1 N HCl buffer at 37 ± 0.5°C. The speed of rotation of paddle was set at 50 rpm. The dissolution tests were carried out for 2 h with sampling time intervals of 5, 15, 30, 45, 60, 75, 90 and 120 min respectively. The samples were analyzed using a double beam UV-spectrophotometer and the absorbance was recorded at 203 nm. The in-vitro dissolution studies were performed in triplicate.[3]

Drug Content

5 tablets were powdered and powder equivalent to 50mg of drug was weighed and taken in a 50ml volumetric flask volume was made with Phosphate Buffer pH 6.0. The solution in the volumetric flask was then sonicated for 20 min and stirred further for 2 hours on magnetic stirrer then filtered using 0.2 m membrane filter. From filtrate, 10 ml of solution was pipette out and diluted up to 100 ml with the phosphate buffer pH 6.0, and absorbance was measured at 203 nm using UV double beam spectrophotometer. [16]

RESULT AND DISCUSSION

FTIR

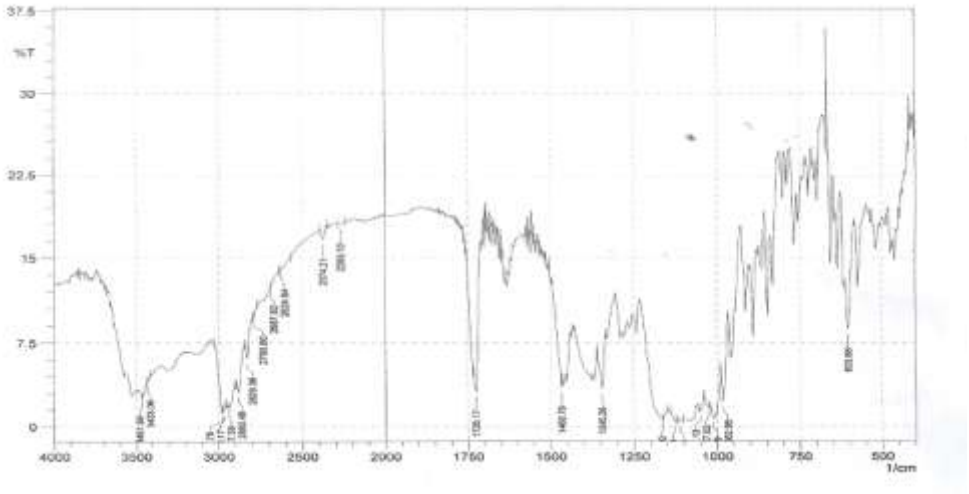

Figure 1 FTIR of Roxithromycin

FT-IR is most useful technique for qualitative compound detection. It gives information about group present in particular compound. Here, Roxithromycin shows a prominent peak at 1726.17 cm-1 corresponding to the –C=O Stretching. FTIR spectra are Roxithromycin compared with the standard spectra given in Indian Pharmacopeia (2007) and it was identical to the standard spectra. So, it proves the purity of the drug.

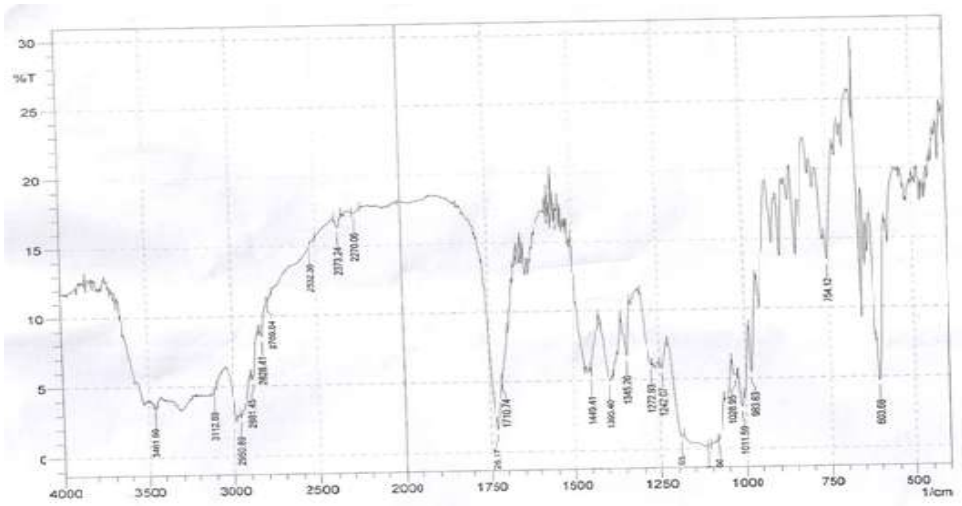

Figure: 2 FTIR of Roxithromycin + Eudragit EPO

FTIR spectra of Roxithromycin, Eudragit EPO, and physical admixture of Roxithromycin plus Eudragit EPO were recorded. FTIR spectrum of Roxithromycin showed characteristic peaks such as 1710.74 cm^{-1}. Thus confirming that, no interaction of drug occurred with the

components of the formulation. The FTIR spectrum of the physical admixture of drug plus polymer showed no significant shift or reduction in intensity of peaks of Roxithromycin. FTIR spectroscopic studies indicated that the drug is compatible with the polymer.

Table 3 Evaluation of microsphere

Batch no.	M1	M2	M3	M4	M5
Angle of Repose(^{0})	31.02±0.12	29.09±0.27	25.24±0.45	27.89±0.25	27.05±0.11
Hausner's ratio	1.29±0.02	1.20±0.08	1.245±0.05	1.288±0.06	1.359±0.05
Bulk Density (g/ml)	0.44±0.03	0.83±0.05	0.57±0.04	0.61±0.06	0.59±0.09
Tapped Density(g/ml)	0.57±0.06	0.91±0.02	0.71±0.07	0.59±0.09	0.51±0.03
Carr's Index (%)	19.80±0.78	17±0.27	14.7±0.69	18.31±.017	20.96±0.64
Total yield (%)	80.66±1.52	82.53±2.43	86.12±2.78	88.56±2.03	86.52±1.48
Drug entrapment (%)	67.6±3.57	71.89±1.64	79.2±2.81	75.46±3.89	77.26±4.96
Particle size (um)	328.79±3.5	414.29±1.76	458.49±2.37	494.26±4.83	534.29±1.67

Taste masking

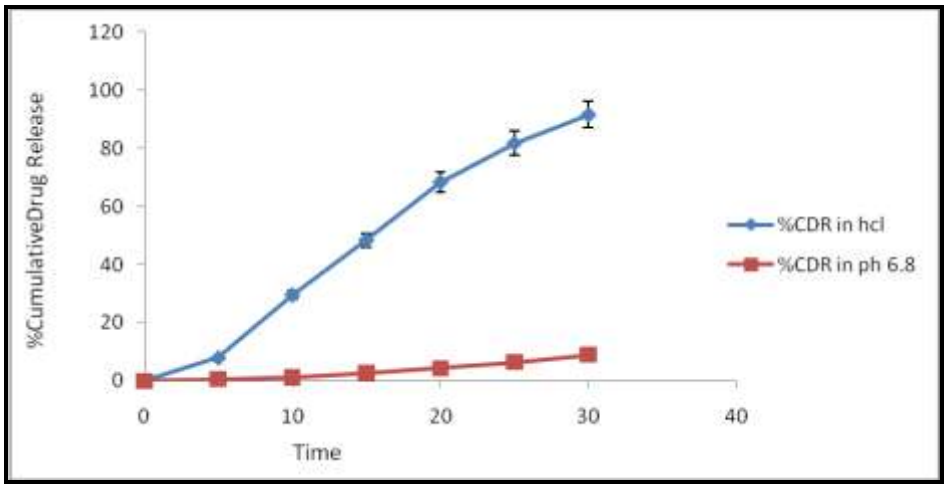

Figure : 3 %Drug release in 0.1NHCl and phosphate buffer pH 6.8

From the graph (figure 3), it was found that in 0.1 N HCl (at gastric pH), more than 90% of drug was released within 30 minutes, Where as in phosphate buffer pH 6.8, less than 20% drug was released within 30 min. Drug release in pH 6.8 phosphate buffer was comparatively slower than that in pH 1.2 medium.

Table 4 Bitterness evaluation of microspheres by panel of 5 volunteers

Volunteer No.	Formulation	Bitterness Level after						
		0sec	10 sec	20 sec	30 sec	40 sec	50 sec	60 sec
1	M1	1	2	2	2	2	3	3
2	M2	1	1	1	1	2	2	2
3	M3	1	1	1	1	1	1	1
4	M4	1	1	1	1	1	1	1
5	M5	1	1	1	1	1	1	1

The volunteers did not report bitterness for microsphere throughout the study. taste Evaluation in volunteers confirmed that the taste of Roxithromycin was masked By preparing microsphere with EEPO ratio 1:3 (drug: polymer). The prepared microspheres were evaluated for flow properties. From results(table 3), it was observed that microsphere having ratio of 1:3 has compressibility index less than 15 %, Hausner's ratio less than 1.25 % and angle of repose less than 30^0. All microspheres prepared having spherical shape. Particle size was indicate that the size of microspheres was increased by increasing the ratio of polymer (EEPO), because of there is fusion between particles produce larger microspheres as the ratio of EEPO increased. Drug entrapment efficiency was determined for different ratios of drug: polymer. It was found that ratio 1:3 gave maximum Drug entrapment efficiency and taste masking also shows good result at the ratio of 1:3.

Table 5 Evaluation of tablet batch T1 toT5

Batch	T1	T2	T3	T4	T5
Weight variation (mg)	209	210	211	210	209
Thickness (mm)	2.33 ±0.025	2.18 ±0.039	2.37 ±0.076	2.24 ±0.033	2.19 ±0.049
Hardness(kg/cm^2)	3.7 ± 0.49	3.5 ± 0.91	3.4 ± 0.48	3.6 ± 0.89	3.5 ± 0.65
Friability (%)	0.92 ±0.037	0.76 ±0.045	0.77 ±0.033	0.89 ±0.047	0.81 ±0.049
Disintegration time (sec)	39 ± 4	38 ± 2	34 ± 1	39 ± 3	35 ± 2
Wetting time (sec)	50 ± 3	47 ± 5	43 ± 2	48 ± 2	45 ± 4
% drug release (30min)	90.21 ±4.86	92.18 ±3.90	94.90 ±4.53	95.52 ±2.36	96.57 ±2.16
Drug content (%)	90.25 ± 3.5	94.66 ± 1.2	92.50 ± 1.5	93.52 ± 2.2	95.15 ± 3.8

All the batches of tablets were evaluated for various physical parameters. Table 4 and 5 includes the values (mean± SD) of weight variation, hardness, thickness, friability, disintegration time, wetting time, % drug content and *in-vitro* drug release of 9 batches prepared using different Superdisintegrants.

All the batches passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight.

Table 6 Evaluation of tablet batch T6 toT9

Batch	T6	T7	T8	T9
Weight variation (mg)	210	209	211	210
Thickness (mm)	2.31 ± 0.017	2.16 ±0.069	2.28 ±0.055	2.17 ±0.041
Diameter (mm)	10.11 ± 0.025	9.86 ± 0.058	9.75 ± 0.84	10.01 ±0.79
Hardness(kg/cm^2)	3.4 ± 0.59	3.5 ± 0.17	3.4 ± 0.91	3.3 ± 0.48
Friability (%)	0.75 ± 0.087	0.8 ± 0.012	0.91 ± 0.045	0.87 ± 0.033
Disintegration time (sec)	26 ± 4 sec	37 ± 2 sec	35 ± 3sec	33 ± 3sec
Wetting time (sec)	41 ± 2 sec	43 ± 1 sec	47 ± 2sec	45 ± 4sec
% drug release (30 min)	98.42 ± 3.48	90.45 ± 2.59	91.39 ± 2.90	93.67±4.53
Drug content (%)	97.69 ± 2.96	91.45 ± 4.57	94.31 ± 3.28	93.84 ± 2.59

Thus, all the physical parameters of the manually compressed tablets were quite within control. Friability values were less than 1% in all cases shows good mechanical strength at the time of handling and transports.

The result indicates that Increase the amount of superdisintegrants decrease in the disintegration time of table. All the tablets disintegrate within 1 min. wetting time is used as an indicator of the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was desirable for ODT. It is also decrease with increase the concentration of superdisintegrants.

***In vitro* Drug release study**

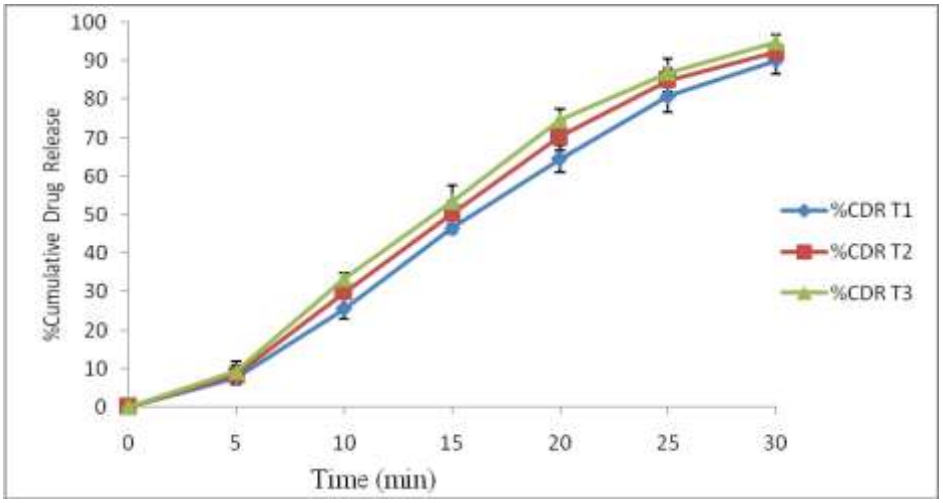

Figure: 4 In-vitro %Drug release of batch T1 to T3 (crospovidone).

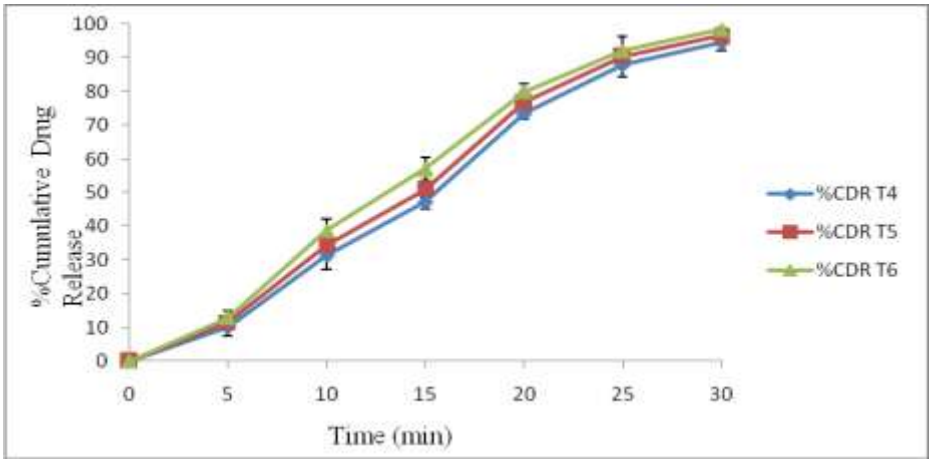

Figure: 5 In-vitro % Drug release of batch T4 to T6 (croscarmellose sodium)

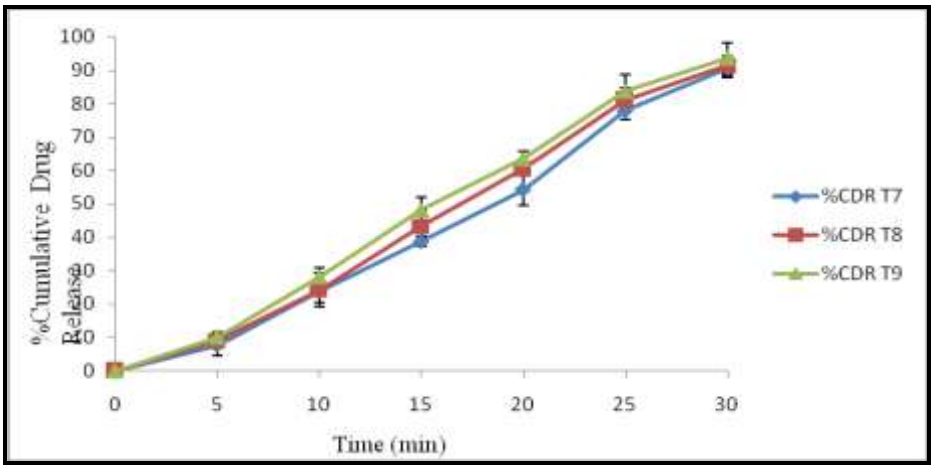

Figure: 6 In-vitro % Drug release of batch T7 to T9 (sodium starch glycolate).

From the graph of all batches it indicates that Drug release was increased by increasing the concentration of superdisintegrants.

Drug content

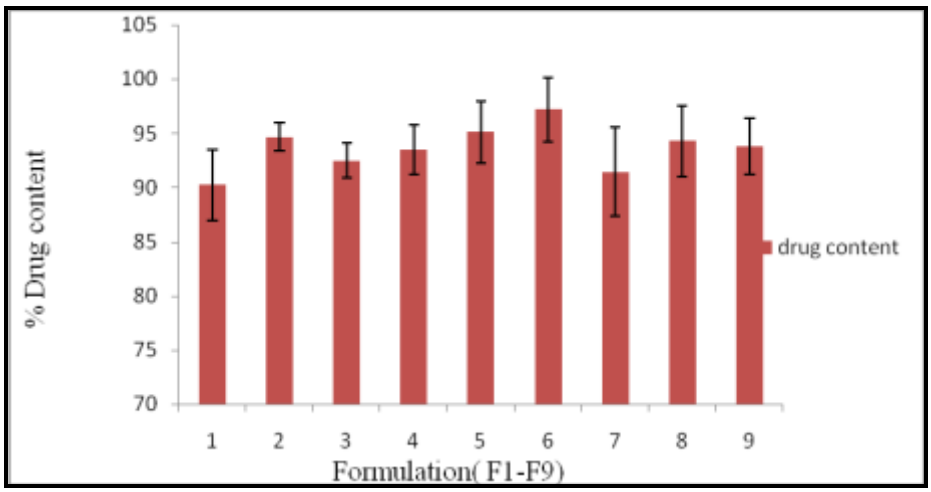

Figure: 7 % drug content

Drug content of all nine formulation measured by UV spectroscopy. From results, all of the batches drug content of F6 batch shows highest drug content compare to other formulation (97.69±2.96).

CONCLUSION

Formulation of Roxithromycin-loaded EEPO microspheres based ODTs gives batter taste masking, rapid disintegration and dissolution of ODTs. especially in acidic medium, in which less than 4.8% was released within half an hour. In addition, formulation of Roxithromycin ODTs containing drug loaded EEPO microspheres improved drug taste. Thus, formulation of Roxithromycin EEPO microspheres incorporated in ODTs could enhance patient palatability, especially in pediatric, geriatric and bed ridden patients.

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